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EPILEPSY AND CEREBRAL PALSY*

BY

BRIAN H. KIRMAN

From the Fountain Hospital, Tooting, London

(RECEIVED FOR PUBLICATION SEPTEMBER 6, 1955)

The two conditions epilepsy and palsy in its many forms are amongst the earliest syndromes recorded in history. The association between epilepsy and cerebral palsy in childhood is a matter of everyday experience, and this association is of scientific interest as throwing light on the nature of cerebral palsy and, more particularly, of epilepsy. It is also of practical importance in view of recent efforts to make more adequate provision for those children with cerebral palsy who are educable. The existence of the two conditions in one child constitutes a double handicap. The present tendency in our educational system is for ever-increasing subdivision of educational 'types', and any child who is difficult to fit into one of the artificial categories thus constructed is in danger of remaining outside the educational system altogether. Epilepsy and cerebral palsy make a difficult administrative problem. Teachers do not much like to have epileptics in their class as they find that the fits are liable to disrupt the work of the class, and epileptic colonies tend to insist on children being able-bodied when admitted for instruction. So the child with both disabilities may be refused admission to one of the few schools for cases of cerebral palsy and also to an epileptic colony. From both the scientific and the practical aspect, then, it is interesting to examine the correlation between these two conditions and to investigate the significance in patients with cerebral palsy of the presence of an epileptic tendency as well. In considering this problem I propose to draw largely on information available about mental defectives, but I believe that what I have to say about these children applies in large measure to others who have not been classed as mentally defective. I have in mind the fact that a child with this double disability is very liable to be classed as mentally defective in any event, irrespective of any further investigation of his mental ability.

* Based on a lecture read at the Institute of Neurology on December 10, 1953.

Frequency of Epilepsy as a Complication of Cerebral Palsy

Brissaud and Souques (1904) attempted to confine the term 'Little's disease' to those cases not complicated by fits or mental defect, but Little's (1861-2) own description of 63 cases refers specifically to the complication of convulsions. Kinnier Wilson (1940) refers to Little's disease not as 'an ailment of a well defined character but a mere syndrome and a rather wide-ranging one at that'. Since epilepsy is also not a disease but a symptom of cerebral dysfunction it is understandable that cerebral palsy and epilepsy should often be encountered in the same patient. Kinnier Wilson states that in his experience 30% of cases of cerebral diplegia have fits which may be general or one-sided. He contrasts this figure with that of 60% of cases of infantile cerebral hemiplegia which, according to his out-patient figures, are so complicated. He quotes Gowers, Fuchs, König, Sachs and Peterson as finding a similar proportion affected.

Cerebral palsy comprises a group of conditions of extremely mixed aetiology and morbid anatomy. The incidence of epilepsy in the different groups naturally varies. For example, the infrequency of convulsive seizures in double athetosis is well recognized (Ford, 1944). Any group chosen for study will have a composition depending on the method of selection employed. The figures for the Fountain Hospital (Table 1) are based on some 806 beds for certified mental defectives, most of them children. Cases of cerebral palsy bulk largely among them and in the majority of such cases the cerebral lesion is probably more gross and widespread than in those children with cerebral palsy who are enabled to attend school. To this extent the incidence and type of epilepsy in these patients with cerebral palsy may have a limited general application. It should be mentioned that in this group cerebral palsy occurs also in association with conditions such as microcephaly, hydrocephalus and the like. Nonetheless, there is considerable

overlapping both in respect of intelligence, pathology and incidence of epilepsy between these patients with cerebral palsy in a mental deficiency institution and those treated elsewhere. The figures for this group therefore have general as well as particular interest.

TABLE
PATIENTS IN FOUNTAIN HOSPITAL GROUP

Total number of patients on books (2.12.53)				777
Total number of cases of cerebral palsy (2.12.53) ..				177 (23%)
Total number of cases of epilepsy (2.12.53)				185 (24%)
Number of cases of cerebral palsy recorded in past 5 yr.				228
Number of cases of cerebral palsy died in past 5 yr. ..				26 (11%)
Of total cases of cerebral palsy				
Spastic diplegia ..	103 (45%)	Epilepsy ..		51 (50%)
Hemiplegia ..	35 (15%)	,, ..		18 (51%)
Athetosis	19 (8%)	,, ..		4 (26%)
Ataxia	5 (2%)	,, ..		0
Unclassified ..	66 (29%)	,, ..		30 (45%)
	228			103 (45%)
Number of cases of epilepsy recorded in past 5 yr. ..				265
Number of cases of epilepsy with cerebral palsy ..				99 (37%)
Number of cases of epilepsy died				49 (18%)

It will be seen from the figures given in the Table that there is a big overlap in this group of institutional cases between epilepsy and cerebral palsy. Apart from mental defect which is common to the group as a whole, epilepsy is the commonest single complication of cerebral palsy, being present in nearly half the cases. The above figures are compiled on the basis of fits which were actually recorded in the Fountain group of hospitals. Many other children had a history of fits before admission, but these are not considered here. Our experience with this group of epileptics with cerebral palsy shows that they share in common with the so-called idiopathic group of epileptics the tendency to have fits when there is present some additional factor in the shape of intercurrent infection, *e.g.*, measles or respiratory disease. Little significance can be attached to the figures of deaths given since the portion of the five-year period during which the individual patients have been classified as epileptics or cerebral palsied varies considerably.

Fits in Different Forms of Cerebral Palsy

The division of the fits among the different forms of cerebral palsy is interesting. As an arbitrary method of classification the dominating symptom has been taken as a basis though naturally some patients present, for example, both spasticity and athetosis. Roughly half the hemiplegics and half the spastics have fits, which is in contrast to the findings of Kinnier Wilson quoted above. On the other hand the strikingly lower proportion of athetotics so affected, roughly one quarter, is in keeping with the general finding. Only five cases have been classified as ataxia, but not one of these has fits. These patients are characterized, in addition to the lack of muscular coordination, by a low muscular tone. Among the group of athetotics, those with 'pure' athetosis are the non-epileptics. The fits occur in those athetoid children who exhibit mixed neurological symptoms, *i.e.*, usually including an element of spasticity which persists in between the athetoid movements. In the case of 'true' athetosis, on the other hand, muscle tone is low or even less than normal when the muscles are not actually engaged in an athetoid spasm. The general impression of a correlation between epilepsy and muscle tone is strengthened by observation of those patients in our hospital group who are not cases of cerebral palsy. A particular example is the case of mongolism. These patients seldom suffer from epilepsy and in them muscle tone is consistently and uniformly low. I have reported elsewhere (Kirman, 1951) the exception which proves the rule, the case of a child with mongolism and cerebral palsy, a rare combination, who was also subject to fits. The fits and the cerebral palsy were both due to infarction of the brain associated with a congenital abnormality of the heart.

Where there is a neurological picture which can be described as cerebral palsy, there is an anatomical lesion in the brain, usually obvious macroscopically, and localized to the extent that it particularly affects some part of the motor system, whether it be the frontal cortex or some sub-cortical centre such as the globus pallidus which is commonly damaged in athetotic syndromes. Such lesions are commonly associated with epilepsy. It would not be true, however, to suggest that brain lesions which have no gross macroscopic localization are not also commonly associated with fits. Mongolism is an exception in this respect, but the less common diffuse disorders of the nervous system such as phenylketonuria and the lipoid disorders are quite commonly accompanied by epilepsy. Thus, out of the 16 cases of phenylketonuria at present in this hospital group, three are complicated by epilepsy. Of these, one has been classified as a case of cerebral palsy. The other 15 patients are all mobile and have no localized palsies. In the few cases of phenylketonuria which have come to post-mortem examination, there has been little macroscopical change, with the exception of Penrose's patient (1939) who had a presumably coincidental neurofibromatosis. Corsellis (1953) does not report any naked-eye abnormality in the brain of his case, that of a phenylketonuric idiot with epilepsy. From his description the case would not in the ordinary way have been classed as one of cerebral palsy, though

'the lower limbs were slightly spastic and her gait was unsteady. All her voluntary movements were clumsy and uncoordinated'.

A child with lipoidosis is also included in the present series as having cerebral palsy of athetotic type. The issue in this patient was complicated by a history of jaundice of the newborn and by the fact that anti-D substance was present in the mother's blood. However, the brain condition at post-mortem examination and the clinical state were compatible with the picture usually found in amaurotic idiocy. The electroencephalogram supported this view.

Of five cases of gargoylism which have recently been in this hospital, none was handicapped by any specific palsy and only one had fits.

Frequency and Relation to Age

As with uncomplicated epilepsy, fits accompanying cerebral palsy tend to fall off in frequency with increasing age. The total number of fits is also often surprisingly small. In many cases there is a history of only a single convulsion. The relationship between the average incidence of fits per year and age is shown for a section of the group of cases of cerebral palsy in Fig. 1.

This graph has been obtained by adding together the number of fits recorded for a given year of age for all the patients of whom a record had been kept at that year and then averaging. The numbers of patients observed under the age of 3 or above 19 was too small to justify compiling an average. The low early incidence of fits, with a subsequent steep rise, is probably due to the change in the character of fits as infancy is left behind. The majority of the young infants with an epileptic tendency in our care rarely have fully developed major convulsions, though they may have a variety of other manifestations, varying from attacks of pallor, dreaminess, screaming attacks, to isolated myoclonic jerkings and unexplained falls. Thus the number of fits recorded in infancy may be small. As the nervous system matures the more adult type of fit which is readily recognizable makes its appearance and is recorded on the epileptic chart.

The decline in the number of fits shown at puberty and after is probably compounded of two parts. On the one hand patients with many fits tend to die. Therefore the survivors tend to be those with fewer fits. On the other hand it is my impression that there is also a tendency for fits to become less frequent in certain patients.

Relation of Epilepsy to Intelligence

It will be appreciated that an adequate record of a thing so elusive as an epileptic tendency is at best unreliable. How much more is this true of such a will-o'-the-wisp as intelligence! There is no general agreement as to the nature of this quality and although it tends to be treated mathematically

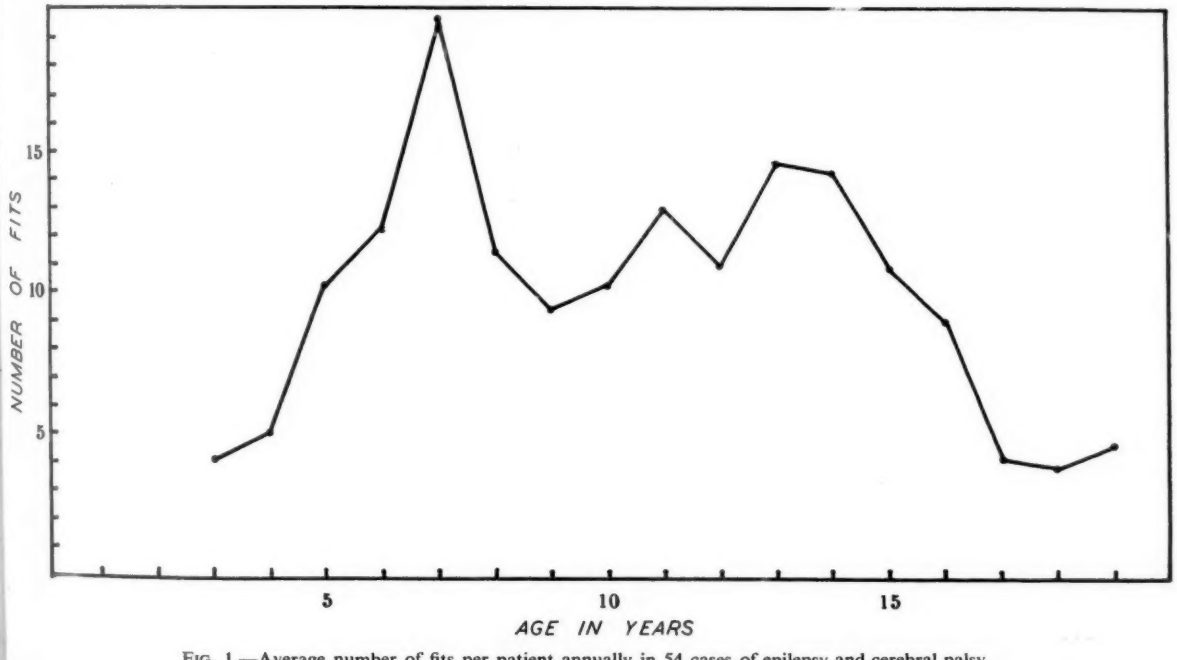

FIG. 1.—Average number of fits per patient annually in 54 cases of epilepsy and cerebral palsy.

as an entity it almost certainly is not. Tests of intelligence are notoriously subject to error even within the normal range. This is much more the case with a special category of children living in institutions with, in the majority of cases, gross brain abnormality.

Formal testing was done on the majority of the patients with cerebral palsy under discussion and the comparative results for the epileptic and non-epileptic are set out in Fig. 2. The significance attaching to these results is necessarily limited. They are records of performance, usually on several different occasions. The heavy overweighting of the sample of cases of cerebral palsy with low-grade patients makes any attempt at differentiation between epileptics and non-epileptics in point of intelligence difficult. In addition, it is notorious that the application of ordinary tests to patients with cerebral palsy is complicated, since such patients commonly have a disability of both hand and tongue, upon the function of which formal tests are based. After giving due weight to all these considerations it may still be thought that the fact that out of 10 patients with an I.Q. above 50 only one is in the epileptic group is significant. Again, taking the figures for those with an I.Q. above 30 the proportion of non-epileptic to epileptic is 3 to 28, *i.e.*, 10%, whereas the proportion for the whole group is 38% non-epileptic. I am indebted to Professor L. S. Penrose for the following interpretation:

> 'The correlation between epilepsy and mental grade in cases of cerebral palsy is $-0{\cdot}17$, with a standard error of $\pm 0{\cdot}08$. The chances of arriving at this distribution by random sampling would be about 1 in 50.'

Additional figures are necessary to enable definite conclusions to be drawn, but this material does point in the direction that would be anticipated. The fact that epilepsy is present in addition to cerebral palsy would suggest the likelihood of a greater general dysfunction of the brain, likely to result in lower intelligence. In the patients with epilepsy the brain lesions are more likely to be cortical, whereas as has been said, some of the non-epileptic cases have neurological syndromes which suggest that there is only minimal involvement of the cortex. It is quite likely that in some patients the epileptic type of activity in the brain, short of actual convulsions or clear-cut petit mal, may interfere with cerebration to an extent sufficient to impair estimated intelligence. In addition, there is the much discussed possibility that damage to the brain with resulting impairment of intellect may result from the effect of fits. Though it has long been accepted (Meyer, 1939) that such is the case, doubt has been cast upon these observations in some instances (Earle, Baldwin and Penfield, 1953; Falconer, 1953), and the view now gaining ground that a number of the lesions recorded, particularly in the temporal area, are the cause and not the result of the epilepsy.

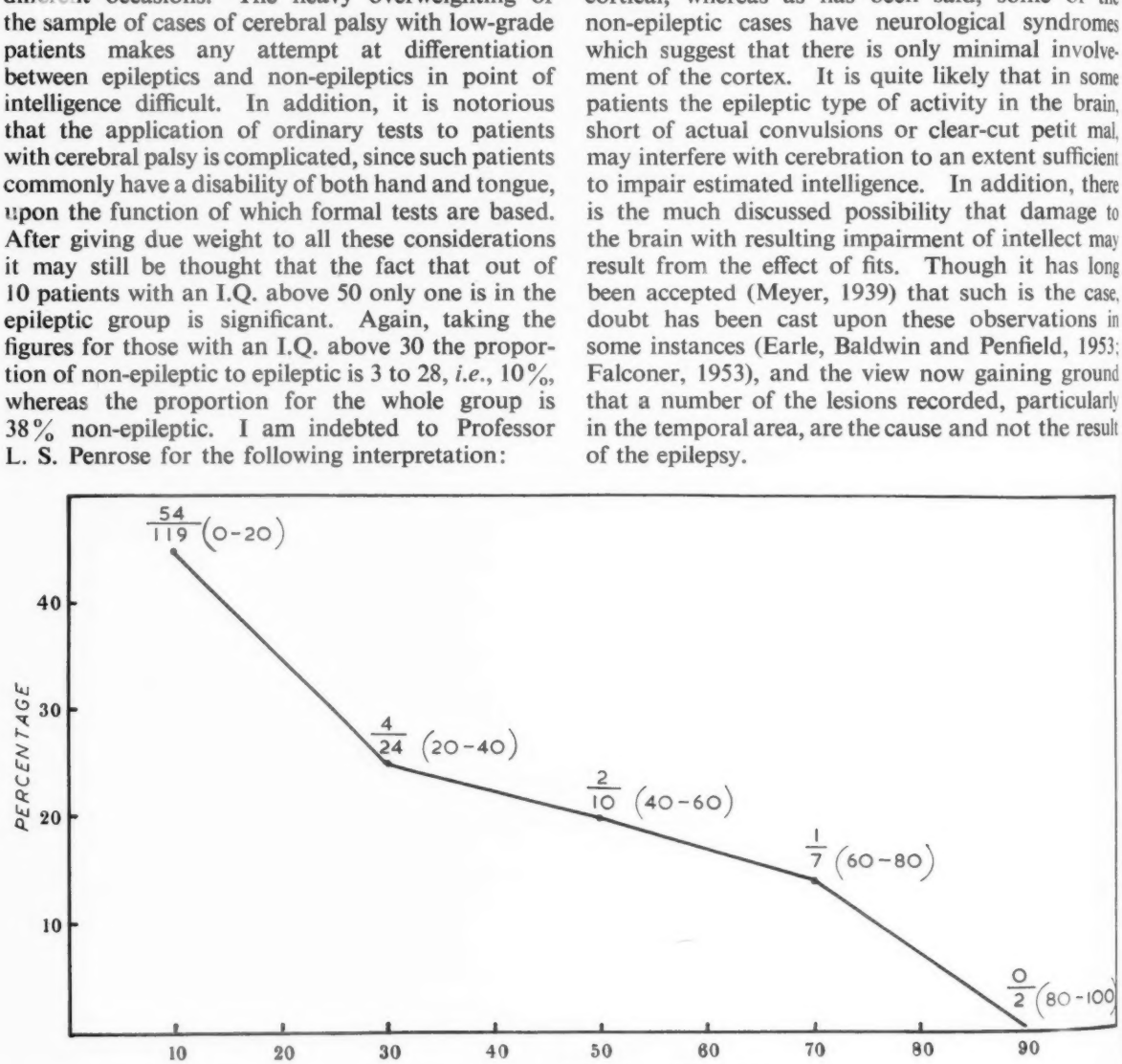

FIG. 2.—One hundred and sixty-two cases of cerebral palsy showing proportion affected by epilepsy at different levels of performance (I.Q.).

Relation to Electroencephalogram

Bridge (1949) states that out of 742 children attending the epilepsy clinic only 30% showed no clinical evidence of brain damage, as assessed from the history, neurological examination and further investigation. (The possibility exists that a large proportion of these 30% also had anatomical brain lesions.) In the case of epileptic children with cerebral palsy clear evidence of a brain lesion is by definition present and it is sometimes possible to assess the situation and extent of the lesion with some accuracy. For this reason electroencephalographic studies on these cases should be particularly useful as a guide to those cases where there is no such clinical evidence as to the situation of the epileptogenic focus.

It is noteworthy that 'epileptic features' in the electroencephalogram are by no means confined to those patients in the group of cerebral palsy with frank clinical epilepsy. Thus J.A.Y. with microcephaly, spastic diplegia and athetoid movements, classed as an idiot, but with no epilepsy whilst in hospital had 'a doubtful focus of sharp waves on the right in transverse recording'.

Another example of a case of cerebral palsy uncomplicated by epilepsy is that of R.L.R. In his case, however, the electroencephalogram showed 'Frequent bursts of moderate voltage sharp waves . . . in runs of two to four waves at a time. They appear to be bilaterally synchronous and symmetrical and there is no definite cortical focus. The lesion responsible for these abnormalities is probably either diffuse or central and basal.' The other remarkable thing about his record is that it was not strikingly abnormal apart from the above findings, although he is an idiot with an estimated developmental quotient of 4. The record, 'a somewhat low-voltage recording, showed alpha, theta and beta activity in about equal proportions in all areas. There is little change on eye opening and closing.'

In the above case it might be postulated that the abnormal activity reported emanated from some central or basal focus as suggested and so interfered with the function of the potentially normal cerebral tissue, though falling short of clinical epilepsy, as to constitute the basis for the idiocy. In fact, however, the existence of the lowest grade idiocy, without the redeeming feature of the alertness and apparent comprehension which sometimes characterizes hopeless cripples, and coupled with a severe spastic diplegia, leads to the conclusion that there is extensive, generalized brain damage, heavily involving the cortex.

R.R.N., another patient with a history of icterus neonatorum not due to rhesus incompatibility, who had an athetoid type of palsy showed 'a doubtfully normal record . . . some good alpha can be seen . . . there is no asymmetry and no epileptic abnormalities'. D.W.T., with an athetoid type of palsy associated with toxaemia of pregnancy in the mother, showed 'no cortical focus and the record is doubtfully abnormal for the age'. S.W. was also a case in the athetoid group without epilepsy. Her condition was attributed to rhesus incompatibility but the damage appeared much more severe than usual, resulting in complete idiocy. In her 'alpha activity can be clearly seen . . . this was symmetrical . . . the slow activity present did not appear to be in excess for the age'.

In sharp contrast with the above findings was E.A.C., who, though having a history of icterus neonatorum, presented with a hemiplegia and clinical epilepsy. His record was 'a grossly abnormal record which is almost entirely occupied by a very high-voltage slow spike and wave . . . This activity is bilaterally synchronous and symmetrical . . . There is no evidence of cortical focus'.

The cases of athetosis resulting from rhesus encephalopathy in general had comparatively normal electroencephalograms. Thus, in the case of P.B. 'a clear dominant alpha rhythm at about 10 cycles/sec. could be seen to block with eye opening . . . the record . . . is probably normal', and in J.L.F. 'alpha activity can be seen at 9 cycles/sec. blocking to eye opening . . . No epileptic features and the record is doubtfully normal.' B.L. has a post-icteric encephalopathy which is not associated with rhesus incompatibility. He showed 'an abnormal record in which only traces of theta activity can be seen and the frequency of which is at the upper limit of normality at about 14 cycles/sec. The dominant rhythm appears to be irregular theta activity which is present throughout the record and has no definite focus in the transverse position. No specific epileptic features . . .' A repeat showed 'good alpha . . . which is symmetrical and blocks well . . .'.

Anatomical studies (Crome, publication pending) demonstrate that the only cases in our group in which the cortex has been relatively spared, and where there was a cerebral palsy, were those patients previously mentioned, with a double athetosis. It is not possible to base general final conclusions on the findings in our group of mental defectives but they provide no evidence to support the suggestion of a sub-cortical driving mechanism in epilepsy. Bilateral features can be explained as due to bilateral damage or, in the case of bilateral synchronous activity, as due to the influence of one hemisphere on the other.

Pathological Findings

In 16 cases from the total group of cerebral palsy information about the state of the brain at post-mortem examination was available. The pathological picture varied very widely. A common feature was reduction in the size of the brain. In addition lesions were usually widespread and involved the cerebral cortex, and often other structures as well. The commonest lesion was a diffuse gliosis.

K.A. had a spastic diplegia and was classed as an idiot. The abnormality developed in early life. Fits began at the age of 2. He died, aged 14, of bronchopneumonia. The brain weighed 1,085 g. Almost the whole brain was gliosed with occipital ulegyria and partial atrophy of the corpus callosum. The ventricles were dilated. The cerebellum and the basal ganglia also shared in the destructive process.

S.M.D. also had a spastic diplegia. Birth was difficult but the child was probably abnormal before birth. Convulsions began in the first few days. The child was classed as an idiot. She died, aged 2, of bronchopneumonia and epilepsy. The brain weighed 560 g. and there was external hydrocephalus with ventricular dilatation. There was generalized gliosis with ulegyria, affecting especially the frontal lobes. Coronal section showed a number of cystic areas corresponding to the situation of the ulegyria. The basal ganglia were also affected by cystic degeneration.

W.C. had no major fits at any time, though there was a query as to petit mal in early life. He had a spastic diplegia, was hopelessly crippled, but appeared to have more comprehension than the other patients mentioned. The head was small. Delivery was instrumental with damage to the head. This was thought to be the cause of the mental deficiency and of the cerebral palsy. He died, aged 10, of carbuncle of the kidney. The brain weighed 895 g. There were numerous areas of induration. The ventricles were dilated. The corpus callosum was thinned. Many of the gyri showed destruction of the normal pattern of the cortex. There was also marbling and patchy cell loss in the corpus striatum and thalamus.

The findings of gliotic encephalopathy in the cases referred to above were typical of the group as a whole, both epileptic and non-epileptic. Usually there was gross involvement of both cortical and sub-cortical structures.

Some cases had more specific features allowing of a more precise estimate of the time of onset of the pathological process. Thus F.N. was an epileptic imbecile with a right hemiplegia. She died aged 4 of status epilepticus. The brain weighed 570 g. There was a left hemiatrophy of the brain with localized microgyria more marked on the left side. The presence of this condition implies that the abnormality occurred early in intra-uterine life.

T.J.R. had a cerebral palsy of the athetoid type which constituted a complete bar to all voluntary activity. There were no fits. He had some understanding. He was not jaundiced after birth. He died, aged 11, of whooping cough. The brain weighed 990 g. The pattern of the cerebral gyri was within normal limits and in general the cerebrum appeared normal, though with a suspicion of increased consistency in the occipital lobes. On the other hand the cerebellum was grossly diseased, being small and indented. The cerebellar cortex was gliosed and the dentate nucleus could not be seen. There was an associated pallor of the ventrolateral nucleus of the thalamus.

P.A.N. showed an example of the malformation of the brain likely to occur as a result of a morbid process beginning in early intra-uterine life. Pregnancy and delivery were normal. He had difficulty in feeding throughout. There was a spastic diplegia of extreme degree and he was microcephalic. However, he had at no time had any fits. He seemed to have some comprehension. He died, aged 18 months, of bronchopneumonia. The brain weighed 530 g. and showed arhinencephaly with failure of separation of the frontal lobes, and absence of the corpus callosum.

J.F.K. was a case of epilepsy and cerebral palsy with brain lesions which may have developed at a much later stage. There was no relevant family history. He was the only child and pregnancy was normal. Delivery was one month premature. He developed slowly and at 3 months was troubled by continuous screaming. The head was large, the fontanelle did not close and he had attacks of 'twitching'. He was of idiot level and had an extreme degree of spastic diplegia. He was considered to be blind. He died, aged $3\frac{1}{2}$, of bronchopneumonia. The brain weighed 290 g. There was external and internal hydrocephalus. The junction of the straight and superior sagittal sinus coincided with a thickening which might have been due to an old thrombus. Almost the entire left hemisphere had been converted into a sac. The right hemisphere was also greatly thinned. Most of the sulci were unrecognizable. The cerebellum was small and flattened.

Summary

Children who have both cerebral palsy and epilepsy are liable to be deemed ineducable and

mentally defective, whatever their intellectual potentialities. Epilepsy in association with cerebral palsy is due to a gross brain lesion. This is probably true of many other cases of epilepsy, including the 'idiopathic' variety. Figures for the Fountain Hospital group based on 806 beds are given. These patients are mainly children certified as mentally defective. Two hundred and twenty-eight cases of cerebral palsy and 265 of epilepsy have been recorded in the past five years. Forty-five per cent of the cases of cerebral palsy were also classed as epileptic (fits observed in hospital). The athetotic and ataxic patients had a low incidence of epilepsy. The frequency of fits in epileptic subjects as recorded increased after infancy but declined with puberty. The evidence suggests that cases of cerebral palsy with epilepsy are likely to be less intelligent on the average than those without this complication. The electroencephalographic recordings show that 'epileptic type' phenomena also occur in patients who have not had fits recorded in hospital. As all the patients in this group, except the small minority of athetotic and ataxic patients, had gross cortical lesions, there is no evidence in this material to support the thesis of sub-cortical epileptic foci. Morbid anatomy showed a wide variety of lesions of which reduction in brain size and gliosis were the most constant. All the brains were very abnormal and most had gross structural abnormalities.

I am indebted to Dr. L. Crome for details of the morbid anatomical investigations and to Dr. D. A. Pond for the electroencephalographic findings. The psychological studies were carried out in the main by Mrs. M. Marrs and Mrs. L. Mundy. Dr. J. H. Crosland kindly provided information on the practical problems involved in the educational placing of children with both epilepsy and cerebral palsy.

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ATTACKS OF UNCONSCIOUSNESS IN ASSOCIATION WITH FUSED CERVICAL VERTEBRAE

BY

R. S. ILLINGWORTH

From the Children's Hospital, Sheffield

(RECEIVED FOR PUBLICATION JULY 11, 1955)

There are more than 140 references in the *Quarterly Cumulative Index Medicus* to papers on fusion of cervical vertebrae, including the Klippel-Feil syndrome. A particularly useful review of the Klippel-Feil syndrome is that by Erskine (1946). He wrote that

> 'Essential features of the cervical deformity are synostosis of two or more cervical vertebrae and flattening and widening of the vertebrae bodies. A numerical reduction of the vertebrae is an incidental rather than an essential part of the disease, as is spina bifida. There is evidence that the anomaly has a genetic basis. . . . Spina bifida is frequently found. It is of a false type, as some of the laminae curve down to meet in the midline in a fused mass in the lower cervical region, so that a triangular opening is found, with the apex directed downward and the base toward the occiput. The triangular deficiency in the arches is covered by a layer of fibrous tissue, and occasionally it extends to the upper thoracic region.'

As a result of the fusion of vertebrae there is limitation of mobility together with shortening of the neck. It may be associated with other abnormalities, such as platybasia, narrowing or asymmetry of the foramen magnum, Sprengel's deformity, scoliosis, torticollis, oxycephaly and cervical rib.

Numerous neurological disturbances have been described in association with the Klippel-Feil syndrome. They include syringomyelia, weakness of the arms or legs, attacks of quadriplegia, abducens paralysis, deaf mutism, cholesteatoma of the cerebellum, nystagmus, facial weakness, sensorimotor changes in the arms, and bimanual synkinesia, or mirror movements, whereby every movement of one hand is imitated by the other hand, so that reciprocal movements like the climbing of a ladder are impossible.

Below are accounts of two children seen on account of attacks of unconsciousness. One was obviously an example of the Klippel-Feil syndrome. The other showed no clinical evidence of an abnormality of the cervical spine, but because of the resemblance of his symptoms to those of the child with the Klippel-Feil syndrome a radiograph of the cervical spine was asked for, and an abnormality was found. I have been unable to find any reference in the literature to such a condition.

Case Reports

Case 1. This was a typical example of the Klippel-Feil syndrome (Fig. 1). She was a girl of 5 years of age with two normal siblings and no family history of a similar

FIGS. 1 AND 2.—Klippel-Feil syndrome, showing the short neck and low hairline.

deformity or of epilepsy. She had a short neck with limitation of movement in it, and there was an associated Sprengel's deformity. Her development had been average. She had learnt to walk without support at 16 months, and at the same age had begun to repeat nursery rhymes. Her speech was average.

She had twice lost consciousness in exactly the same circumstances—when she was trying to reach something above her head. In each case she dropped unconscious, white in the face, and did not twitch or feel stiff. After a minute she was normal and running about. There were no abnormal physical signs in the central nervous system, fundi or elsewhere. The radiograph of the cervical spine is shown in Fig. 3. There was a spina bifida of the upper dorsal vertebrae, with a congenital deficiency of the right halves of some of the cervical vertebrae. The bodies of the cervical spine, which was foreshortened, were completely fused. The right scapula was elevated, and there was a congenital absence of the first left rib. The upper two dorsal vertebrae were also fused.

It was assumed that the attacks of unconsciousness were associated with the abnormality of the spine, and no specific treatment was prescribed.

She was seen again at the age of $8\frac{1}{2}$ years. She had had a third attack of unconsciousness two years and a fourth a year previously. On one occasion she was having breakfast and on the other she was being dressed. The parents were not clear exactly what movement the girl performed immediately before the attacks. In each case she was unconscious for one or two minutes, and was pale, perspiring, but not twitching. It was felt that these two attacks might have been epileptic in origin, but the electroencephalogram was entirely normal.

FIG. 3.—Case W.B.: Cervical spine.

Case 2. This boy (Fig. 4) was referred at the age of 4 years by Dr. Steiner on account of attacks of unconsciousness following injuries to the back of the head.

FIG. 4.—Case J.R., showing apparently normal neck.

The boy was adopted, and it was therefore impossible to obtain a family history.

The story was that whenever he had a knock on the back of the head he became unconscious. The first attack was at the age of 7 or 8 months. He had just begun to sit up, without help, and on one occasion he fell over backward and became unconscious. He was cold and clammy, and remained unconscious for five to 10 minutes. There was no stiffness or twitching. The adopting mother thought that he was dead. He recovered consciousness, was dazed for a few seconds, and then behaved normally. From that time onwards there were at least 12 occasions on which he had exactly similar attacks immediately following an injury to the back of the head. He never had any attack without such an injury. The mother was convinced that the unconsciousness never preceded the falls. On one occasion he collided with a boy, hitting the back of the head, and fell unconscious. On many other occasions he had injuries to the front or side of the head, but never became unconscious. On one occasion he fell off his tricycle on to a concrete path and hurt the front of his head severely, much more severely than he had ever been hurt on the back of his head, but he did not become unconscious. Immediately after recovering consciousness after each attack, he did not go to sleep, but got up and went on playing as if nothing had happened. There is no breath-holding at the beginning of the attacks and there is no cyanosis, stiffness, twitching or incontinence. Owing to the attacks he is not allowed to go out into the playground at school to play.

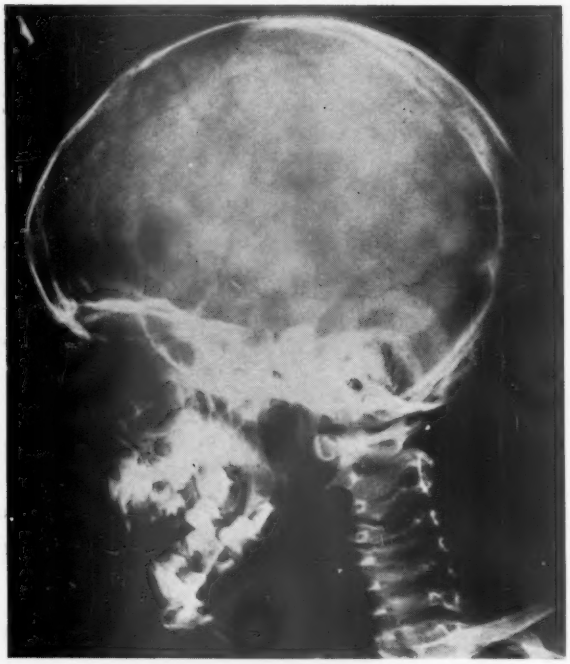

FIG. 5.—Case J.R., radiograph of the skull and cervical spine. The skull is apparently normal. Fusion of second and third cervical vertebrae is shown.

FIG. 6.—Enlarged view of fused cervical vertebrae of Case J.R.

There was no history of headaches, vomiting, easy bruising or temper tantrums. He was a boy of average intelligence, who had developed normally. He had begun to walk without help at the age of 15 months. He had acquired full sphincter control, day and night, by the age of 3.

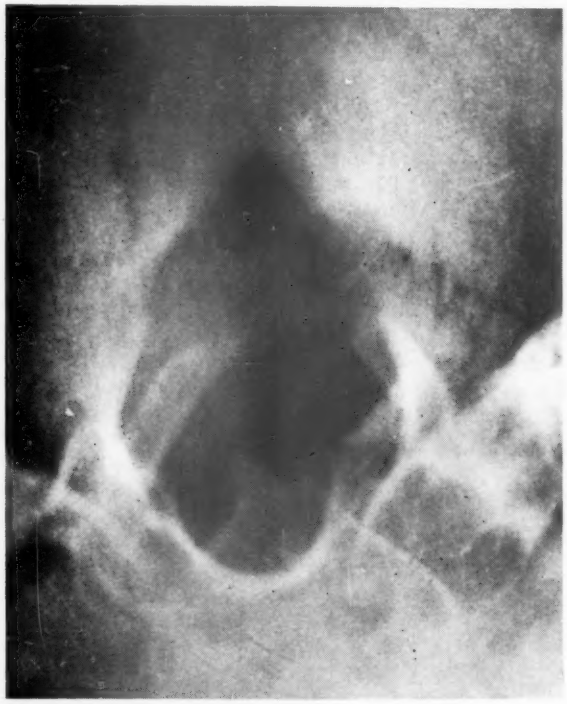

FIG. 7.—The abnormal foramen magnum in Case J.R.

On examination no abnormality was found. The fundi were normal. The pulse rate was 64 per minute. The cerebrospinal fluid was normal. The radiograph of the skull was normal, but the radiograph of the cervical spine showed fusion of the laminae and spinous processes of the second and third cervical vertebrae (Figs. 5-7). The foramen magnum was enlarged backwards. There was a spina bifida occulta of the atlas. A spinal myelogram did not add any information. The haemoglobin was normal (14·1 g. per 100 ml.). Only after the radiograph of the cervical spine had been seen was it thought that there was a very slight limitation of full flexion of the neck.

The electroencephalogram was normal. Movement of the head from full flexion to extension and vice versa had no significant effect on the electrical activity of the brain. The electrocardiogram was normal. Sudden flexion of the neck did not precipitate an attack, but we did not try the effect of hitting the boy on the back of the head.

Discussion

In an extensive search of the literature I was unable to find a reference to attacks of loss of consciousness in persons with anomalies of the cervical spine. The problem was referred to Professor A. J. E. Cave, of the Department of

Anatomy, St. Bartholomew's Hospital Medical College, London, for advice. He pointed out that the only common factor in the two children seemed to lie in sudden interference with medullary activity, either mechanical or vascular. He felt that the attacks of unconsciousness were most unlikely to be of vascular origin, because of the remarkable way in which arteries are 'able to fend for themselves' in the presence of anomalies of bone. He thought that the attacks were much more likely to be of mechanical origin. He commented, concerning the second case, the boy J.R.:

> 'The fusion of the neural arches of cervical vertebrae 2 and 3 is by itself insignificant. The radiographs show, however, an anomalous foramen magnum outline, a dorso-median extension or notch which is not infrequently encountered in cases of congenital defect of the cranio-spinal region. It seems that the medial ends of the neural arch moieties of the atlas encroach somewhat upon the customary vertebral arch outline, and at 6 years one would have expected their mid-dorsal union, incompletely at least. If this is so, the median enlargement of the posterior border of the foramen magnum may be in the nature of a compensatory accommodation of the medulla, which extends inferiorly to the upper edge of the atlantal posterior arch. So far as I can judge, this child manifests some unusual congenital condition of the occipito-atlantal region, in the nature of a posterior modification of skeletal parts to accommodate the medulla. Falls or blows to the occipital region must bring the medulla sharply and intimately into contact with the posterior parietes of the occipito-vertebral region, with resulting black out. As regards the girl, W.B., the radiograph shows a very disorganized cervical spine, and I doubt not that the foramen magnum region is also congenitally anomalous.'

He went on to remark that we have no assurance that the central nervous system is normal in such cases, adding: 'It would not be surprising if medullary defect should accompany constitutional defect of the relative and enclosing skeletal parts'.

It is interesting to note that the reaction of the two children was identical—sudden unconsciousness without stiffness or convulsive movements, immediately followed by normal activity and running about without drowsiness. In the girl the third and fourth attacks suggested the possibility of epilepsy, and that diagnosis cannot be entirely excluded in spite of the normal E.E.G. In the case of the boy there is nothing to suggest epilepsy, and it is clear from the history that all attacks immediately followed injuries to the head, and that the injuries did not result from an attack of unconsciousness. The cause of the attacks remains obscure, but Professor Cave's suggested explanation, namely sudden compression of the medulla, seems to be the most likely one.

Summary

Two children with attacks of unconsciousness associated with anomalies of the cervical spine are described. In one case, a typical example of the Klippel-Feil syndrome, attacks of unconsciousness followed extension of the neck: in the other case, attacks of unconsciousness followed sudden flexion of the neck caused by blows on the back of the head. The children were pale and limp in the attacks, without convulsive movements, and ran about normally immediately on recovery of consciousness.

The possible anatomical cause of the attacks is discussed.

My especial thanks are due to Professor A. J. E. Cave for going to a great deal of trouble in searching the literature, and examining his notes, correspondence and museum specimens to find an anatomical basis for the attacks described, and for giving permission to quote his letter.

I also wish to thank Dr. T. Lodge, radiologist, for the radiographs, Dr. J. W. Warboys for the E.E.G.s, Drs. J. W. Steiner and D. E. Hobday for referring the children to me, and to Professor F. Davies for his advice.

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NEPHRITIS IN CHILDHOOD

A CLINICAL ASSESSMENT OF THE ELLIS CLASSIFICATION

BY

NORMAN S. CLARK

From the Department of Child Health, University of Aberdeen

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Although it is now well over 100 years since Richard Bright described that group of diseases to which his name is still attached, no final agreement has yet been reached on their proper definition and classification. It is true that chronic pyelonephritis and essential hypertension have been defined as conditions clearly distinct from true nephritis in respect of their aetiology and early course, but nephritis itself, despite a multitude of classifications of varying degrees of complexity, still awaits a final analysis. Various and often multiple adjectives have been added to the word 'nephritis' in succeeding attempts to subdivide the condition into separate groups or entities, but it is notable that, of the many classifications proposed, not one has proved universally acceptable to both clinicians and pathologists.

The classification probably most widely used in this country at present is that of Ellis (1942) in which Bright's disease is subdivided into nephritis, essential hypertension and 'miscellaneous conditions' in which 'the renal disorder is incidental to some other disease'. Ellis regards nephritis itself as divisible into two clearly defined types differing in aetiology, clinical features, histology and prognosis. He defines type 1 nephritis as an illness of acute onset, usually at a short interval after an acute infection, with haematuria as the most prominent and constant symptom, and in many cases some degree of hypertension and oedema. The majority of cases ultimately recover completely. Type 2 nephritis he describes as a disease of insidious onset characterized by generalized oedema, gross albuminuria, a progressive course and a uniformly bad prognosis. His terms 'type 1' and 'type 2 nephritis', carrying with them the implication of two separate and distinct diseases, are now in very wide use in the British medical literature but, so far as I know, the only critical appraisals of Ellis's views have been those of Davson and Platt (1949) and Enticknap and Joiner (1953). Both papers report a few cases which do not fit easily into type 1 or type 2 of Ellis's classification. Davson and Platt, while reserving judgment on whether type 1 and type 2 are separate entities aetiologically, consider that 'as a practical classification of nephritis the Ellis classification is an advance', while Enticknap and Joiner conclude that 'this classification has little to recommend it from a descriptive point of view'.

Some years ago, in the course of a clinical trial of an antihistamine drug in the treatment of nephritis, I had occasion to extract and study the records of 265 consecutive cases of nephritis admitted to the Royal Aberdeen Hospital for Sick Children. The considerable difficulty experienced in fitting all the cases into two separate and clearly defined types prompted further consideration of these cases in the light of the Ellis classification. This analysis has been, of necessity, purely clinical, for comparatively few patients died and the amount of necropsy material available was quite insufficient to form the basis of any criticism of the Ellis classification from this angle. The clinical details, including the results of a long-term follow-up, are sufficient, however, for a clinical study of the natural history of nephritis originating in childhood, and the results of this study are here presented with particular reference to the validity of the Ellis classification from the clinical standpoint.

Material

This survey covers all cases admitted to the Royal Aberdeen Hospital for Sick Children between April, 1934, and May, 1952, in which a final diagnosis was made of 'nephritis' of any variety (excluding, of course, pyelonephritis). I have personally seen all cases admitted subsequently to January, 1946. The information on cases admitted before this date is derived entirely from the case notes.

During this period a final diagnosis of nephritis has been made in 265 cases. In addition, eight children when first seen were all in varying stages of renal failure with azotaemia, polyuria and urine of fixed, low specific gravity. This syndrome in childhood is probably less frequently due to true chronic nephritis than to congenital abnormalities of the kidney or to chronic urinary infection (Clark, 1951). Congenital abnormalities of the kidneys were found at necropsy in several of these eight cases, and in none of them was there any history of a previous attack of nephritis. As there is no clear evidence that any one of them represents the terminal stage of true nephritis, I do not propose to consider them here.

During the period of this survey the diagnosis 'nephrosis' does not appear in the disease index; no case, therefore, has been excluded as being an example of this condition.

Of these 265 patients, 20 died in the initial illness and three are known to have died subsequently. Attempts to assess the final outcome of the disease by follow-up examination were successful in 156 patients, and information was received from various sources on the present state of a further 19 who could not attend for examination. The interval from the onset of symptoms to the final follow-up examination varied from one to 13 years (in only 13 cases was it less than two years). Sixty-seven cases remain untraced.

Classification

Of the 265 cases, 239 conform closely to Ellis's description of type 1 nephritis; they had an illness of acute onset, usually at an interval of one or two weeks after an acute infection, with haematuria as the most constant symptom and some degree of hypertension and oedema in many cases. One proviso must be made to this statement, however, namely that Ellis and certain other workers might classify some of these cases as 'acute focal nephritis'. Ellis specifically excludes from his cases of type 1 nephritis 35 cases of acute focal nephritis and puts them under the heading of miscellaneous conditions in which the renal symptoms are incidental to some other disease.

The term 'acute focal nephritis', first proposed by Volhard and Fahr, has been widely used to cover a type of case in which haematuria appears at the height of an acute infection and is not accompanied by either oedema or hypertension. This condition is described in some detail by Fishberg (1954) who maintains that hypertension and oedema are consistently absent throughout the course of the disease and that the prognosis is invariably excellent. He considers that these cases resemble acute nephritis superficially only. While Ellis apparently also feels that this is a separate entity and excludes such cases from his group of type 1 nephritis, he states that in two of his 35 cases 'albuminuria persisted between the attacks and after many years the blood pressure rose and death occurred in renal failure'. As 10% of his cases of type 1 nephritis followed a similar course, it seems that the long-term prognosis in both groups is substantially the same, a finding at variance with Fishberg's opinion that the prognosis in acute focal nephritis is always excellent. As Ellis does not claim that hypertension and oedema are always found in cases of type 1 nephritis, the grounds for differentiation between this type and acute focal nephritis appear to be slender.

Careful consideration of the case records of the present series leads me to agree unhesitatingly with Payne and Illingworth (1940) that there are no clinical grounds whatever for distinguishing acute focal nephritis as an entity. Those case histories which show an interval of less than one week between the onset of an acute infection and the appearance of the first signs of nephritis have been scrutinized with particular care; they show all gradations of severity in the initial illness and hypertension has been marked in many of them. Conversely, scrutiny of the records of those who have shown neither hypertension nor oedema at any stage of their illness shows no relationship between these features and onset at the height of an acute infection, and indeed many of these cases showed no evidence at all of active infection on admission.

In five (2%) of the 239 cases haematuria was consistently absent on daily microscopic examination of the urine during the first week in hospital. In their initial picture and subsequent course these cases appear to fit into type 1 in every other respect, and it seems, therefore, that even haematuria is not an absolutely constant finding in the early stages.

No other significant difference from Ellis's description of the symptoms and course of type 1 nephritis was noted in any of these cases.

In two cases the information available from the notes is too scanty to permit of definite classification.

There remain, therefore, 24 cases which cannot at once be accepted as examples of type 1 nephritis. The histories of these cases (summarized in the Appendix) must now be considered. To simplify discussion they are presented in four groups, all the members of each group having certain features in common.

Group 1. These four cases have all presented a rather similar picture. All had gross oedema with effusion in one or more of the serous cavities, persisting, except in Case 183, over several months. A15 and A23 had a marked rise in blood cholesterol and 183 showed a reversal of the albumin/globulin ratio. All showed a persistent very heavy albuminuria. While these features are more commonly associated with type 2 nephritis, the other findings would seem to place these four cases as severe examples of type 1. Nevertheless, Case 68 died 10 years after her original illness and Cases 183, A15 and A23 are alive and in fair health, though with evidence of persisting renal damage after two or three years, as against the few months which Ellis quotes as the usual course of type 1 nephritis, showing gross and persistent oedema.

Group 2. These six cases again show certain general resemblances to one another. Cases 123, 151, A14 and A37 had no history of recent infection and Case 9 a doubtfully significant history. Repeated microscopic examination showed no red blood cells in the urine of Case A8, and red blood cells were scanty and only occasionally found in Cases 123, 151, A14 and A37. In the remaining case the only microscopic examination noted showed me red blood cells. All cases showed a raised blood cholesterol level except Case A8 in which this investigation was not carried out. Cases 123, A14 and A37 had gross oedema and Cases 151 and A8 moderate oedema. These features and the unexplained purulent abdominal effusion in Case 151 are all more in keeping with Ellis's type 2 nephritis than with type 1. While the type 2 features are more prominent in this group than in the previous one, all cases still bear many resemblances to type 1 and probably some workers who use the Ellis classification would accept them in this category.

Group 3. These six cases should probably be placed in type 2 of Ellis's classification but they all show certain unusual features. Cases 41, 201 and A32 had a history of acute respiratory infection one or two weeks before nephritic signs appeared. The initial illness of Case 41 conformed closely, apart from its relatively brief course, to Ellis's description of type 2 nephritis, but on her second admission there is a very clear history of macroscopic haematuria at home, although in hospital blood was only seen microscopically. Case 117 had macroscopic haematuria in hospital on two occasions and his blood pressure remained elevated for over three months. Both these patients were alive and clinically well with normal urine 10 and seven years respectively after the onset of their illnesses.

Case 201 had a fairly clear-cut history of an attack of type 1 nephritis three months before admission, but his course in hospital was that of type 2. Case A31 is difficult to classify with certainty because she was admitted to hospital late in her illness when the oedema had already disappeared. On the whole the findings were more in keeping with type 2 nephritis, but again there was a history of 'red' urine at the onset.

Case A32 for four months after admission ran a type 2 course and then developed persistent haematuria which was occasionally macroscopic; although his plasma proteins twice fell to 3·5 g. %, they were frequently normal and his albumin/globulin ratio was never reversed. Case A36 on his first admission also presented a type 2 picture, but on re-admission had macroscopic haematuria.

Thus all six cases showed gross haematuria at some stage of their course which, according to Ellis, is rare in type 2 nephritis. Case A36, the only one to come to necropsy, showed certain features of both types of nephritis.

Group 4. The eight cases in this last group conform fairly closely in the nature of their initial illness to Ellis's type 2 nephritis, but their course has not shown the steady downward progress which he describes as characteristic of the disease. Four of these children showed no evidence of persistent renal damage when examined from one to five years after the onset of their illnesses, and another is known to be alive and apparently well after three years, although it was not possible to examine her or to obtain a specimen of urine. Two died in their initial illness and only one (Case 145) has shown evidence of continuing renal disease. While the number of cases is too small to justify any firm conclusions regarding prognosis, the results are obviously less uniformly gloomy than in Ellis's large series of 145 cases in which only five recovered. Ellis also lays some stress on the infrequency of a history of antecedent infection in cases of type 2 nephritis (less than 5%); it should be noted that five of the above eight cases have a fairly clear history of upper respiratory infection shortly before the onset of nephritic symptoms.

If we try to fit the cases in this series into the Ellis classification it appears, therefore, that of the 24 cases which cannot be accepted as definite examples of type 1 nephritis, only eight appear to fall clearly into type 2. The remaining 16 cases can only be accepted in either type with certain reservations, and in all of them the clinical picture lies somewhere between the picture of type 1 nephritis and that of type 2 nephritis.

Discussion

Ellis's contention that nephritis can be divided on clinical grounds into two clear-cut types is not upheld by the findings in this series. The general impression left after the consideration of these cases is that nephritis presents a complex and infinitely variable clinical picture with, at one end of the scale, a large group of cases in which the dominant features are acute onset and haematuria and, at the other end of the scale, a small group of cases in which the dominant features are sub-acute onset, oedema and albuminuria, while between these two extremes lie a number of cases which cannot be formed into a homogenous group or groups but which show varying combinations of the symptoms presented by the cases at both ends of the scale.

After consideration of the clinical features of the present series of cases, I find myself in general agreement with the view of Enticknap and Joiner quoted above that 'this classification has little to recommend it from a descriptive point of view'. While it may be useful from the point of view of prognosis and management to subdivide cases of nephritis into two groups, I feel that this should be regarded as a matter of clinical convenience and not as implying any hard and fast distinction between two different diseases. There is, I think, much to be said for reverting to the older titles of 'acute haemorrhagic nephritis' and 'sub-acute oedematous nephritis' which are generally descriptive of the usual clinical pictures and do not carry the implication of a fundamental distinction between two different diseases.

In my view the varied clinical pictures in the present series can only be explained on the assumption that they are different expressions of one indivisible disease process. This is, to a large extent, the view of Snoke (1937) and Payne and Illingworth (1940), but with one difference which is, I think, of some importance. They, in common with most workers, who do not regard the oedematous type as a separate disease, consider it to be a stage in the development of nephritis, a sequel to a previous attack of acute haemorrhagic nephritis. They suggest that the absence of a history of a previous frank attack of acute nephritis in many of their oedematous cases can be explained on the assumption that there has in fact been a previous attack so mild as to remain undetected. That acute nephritis may, on occasion, be so mild as to escape detection without careful examination of the urine is undoubtedly true, but there seems no good reason to suppose that such mild attacks are more likely to be followed by the subacute oedematous picture than are more obvious and severe attacks. Yet this assumption of a previous unrecognized acute attack must be invoked in the great majority of cases of oedematous nephritis if this condition is to be considered as a later stage in the evolution of nephritis, for the incidence of recognized previous attacks of acute nephritis has been even lower in most reported series than the 33% quoted by Payne and Illingworth. This assumption is, by its very nature, insusceptible of proof, nor is there any convincing indirect evidence to support it, and it is not surprising that its validity has been questioned. Indeed, the absence of a history of an antecedent frank attack of haemorrhagic nephritis in the great majority of cases of oedematous nephritis has been used as an argument by those who consider that the two conditions are different diseases.

If, however, instead of regarding acute haemorrhagic nephritis and subacute oedematous nephritis as different stages of the same disease, we regard them as different expressions of it, no such assumption is necessary and this conception is certainly more in keeping with the occasional case such as Case 41 (and possibly also Cases A32 and A36) in which the initial picture was that of oedematous nephritis while, at a later stage, the symptoms were those of the haemorrhagic type.

Of the factors which determine the mode of expression and the probable course of nephritis in the individual case we are still largely ignorant, and until our knowledge of the underlying pathological processes is considerably extended, it appears that attempts to subdivide the manifestations of nephritis are more likely to confuse than clarify our understanding of the problem.

Summary

The case histories of 265 cases of nephritis in childhood have been reviewed and an attempt made to subdivide them into two types in accordance with the Ellis classification.

While 239 cases conform fairly closely to Ellis's description of type 1 nephritis, only eight can with certainty be described as type 2 and of these at least four appear to have made a complete recovery.

The remaining cases appear to fall somewhere between the two types and it is suggested, therefore, that type 1 and type 2 nephritis are not, as Ellis suggests, different diseases, but merely the two extremes of a single clinical picture which is capable of very considerable variation. It is further suggested that, if nephritis is to be subdivided at all, this can only be done at the descriptive level and as a matter of convenience, and that there is much to be said for reverting to the older titles of 'acute

haemorrhagic nephritis' and 'sub-acute oedematous nephritis' which do not carry the implication of a distinction between two different diseases. The pictures which these titles describe appear to be different expressions rather than different stages of the same disease process.

APPENDIX*

Group 1

Case 68. A girl aged 10 years was admitted on August 12, 1937, with a history of generalized oedema of gradual onset about four months previously. One month or less before the oedema was first noted, she had a febrile illness diagnosed as 'influenza'. No haematuria was noticed at home. On admission she showed marked generalized oedema with effusion in the right chest; blood pressure 140/108 mm. Hg; blood urea 57 mg. %; urine, albumin ++, and on deposit, red blood cells. Hypertension and microscopic haematuria persisted thoughout eight months in hospital. Her blood pressure rose to a maximum of 190/130 mm. Hg and haematuria was at times macroscopic. Oedema increased for the first three months, then gradually disappeared in the next two months, in which her weight fell from 91½ lb. to 70 lb. She died at home in uraemia 10 years later.

Case 183. A girl aged 10 years was admitted on June 10, 1946. Three weeks previously she had a mild attack of scarlet fever; one week later the legs and abdomen began to swell and she complained of persistent headache. On admission she had generalized oedema and ascites; blood pressure 150/100 mm. Hg; blood urea level 172 mg. %; urine, albumin +++, and on deposit, red blood cells. The oedema disappeared after one month and the blood pressure fell to 100/70 mm. Hg in six weeks, but the blood urea level only once fell below 40 mg. % in 11 months in hospital. Very heavy albuminuria and haematuria that was at times macroscopic persisted. The plasma proteins on two occasions showed albumin/globulin ratios of 0·87/1 (total protein, 4·66 g.) and 0·80/1 (total protein, 4·94 g.). When last seen two and a half years after the onset of her illness she was in fair condition; the blood pressure was 110/60 and the blood urea level was 34 mg. %, but she still had heavy albuminuria.

Case A15. A girl aged 11 years was admitted on February 28, 1949. She had no history of recent infection. Two weeks before admission she complained of headache, passed dark brown urine, and was thought to have a puffy face. On admission there was oedema of the face only; blood pressure 110/80 mm. Hg; blood urea, 30 mg. %; urine, albumin +++ and macroscopic blood. The oedema became generalized and ascites appeared. The blood pressure remained normal and the blood urea level rarely rose above 40 mg. %; the blood cholesterol level rose to 446 mg. %. Albuminuria continued gross; Esbach readings on 24-hour specimens on 18 occasions were almost invariably above 5 parts, and on one occasion rose to 22 parts. Haematuria persisted (and was at times macroscopic) throughout her eight months in hospital. When last seen over two years after the onset of her illness she was in fair general condition; her blood pressure was 118/75 mm. Hg; blood urea, 24 mg. %; the urine contained albumin++ and scanty red blood cells. She has had several flare-ups with gross haematuria in the interval.

Case A23. A boy aged 4 years was admitted on July 20, 1949. Three weeks previously he developed a sore throat followed after an interval of two weeks by the appearance of generalized oedema, by repeated vomiting, and by the passage of dark urine. On admission he showed generalized oedema with ascites and a left pleural effusion. His blood pressure was 126/84 mm. Hg and his blood urea level 33 mg. %. His urine contained albumin (6 parts Esbach) and macroscopic blood. The oedema increased and became very gross, his maximum weight, two months after admission, being 57 lb. His blood pressure at this time rose to 140/106 mm. Hg. Following hot packs and abdominal paracentesis he lost 10 lb. in weight in 10 days, and four months after admission he weighed 35 lb. and there was no detectable oedema. His blood pressure remained slightly elevated. Throughout seven months in hospital albuminuria and microscopic haematuria persisted. The blood cholesterol level at one time reached 504 mg. %. Two and a half years after admission he was well and attending school regularly. His blood pressure was 120/80 mm. Hg, the urine contained persistent traces of albumin and an Addis count on a 12-hour specimen showed 2,970,000 red blood cells.

Group 2

Case 9. A girl aged 3 years was admitted on August 29, 1934. Two months before admission she developed measles, after which she was left with enlarged tonsillar nodes. Four days before admission her face became puffy and her urine contained albumin. On admission she had doubtful oedema of the face only and her charts show no loss of weight during her six weeks in hospital. Her blood pressure was 108/80 mm. Hg, her blood urea level 45 mg. % and blood cholesterol 350 mg. %. The urine contained albumin++ and microscopic examination showed many casts but no red blood cells. Unfortunately there is no record of any subsequent microscopic examination, but the albuminuria diminished and ceased entirely after three weeks. Her subsequent history is unknown.

Case 123. A girl aged 11 years was admitted on November 10, 1941. There was no history of recent infection. Three weeks before admission she developed swelling of the face, vomited repeatedly, complained of pain in the abdomen and back, and passed scanty dark urine. On admission she showed extensive oedema;

* Cases are numbered consecutively in the order of their admission. The last 62 cases admitted are numbered A1 to A62; this division into two series is of no significance for the purpose of the present paper.

her blood pressure was 130/94 mm. Hg and blood urea level 42 mg. %. The urine contained albumin++ and macroscopic blood. Fairly heavy albuminuria continued throughout eight months in hospital but haematuria diminished rapidly and repeated microscopic examination subsequently showed no red blood cells. The blood cholesterol level varied between 432 and 700 mg. %. Oedema fluctuated throughout her stay in hospital and was at times gross and generalized and at times absent. She died at home one year after the onset of her illness.

Case 151. A boy aged 8 years was admitted on July 14, 1944. He had no history of recent infection. One week before admission his legs began to swell and he vomited repeatedly and passed scanty urine containing albumin. On admission he showed oedema of the face and legs; his blood pressure was 124/90 mm. Hg, his blood urea level 87 mg. %, and blood cholesterol 328 mg. %. The urine contained albumin+ and red blood cells on microscopic examination. Ten days after admission the abdomen became swollen. Next day paracentesis produced 1 pint of greenish turbid fluid, sterile on culture but containing many polymorphs. (No chemotherapy had been given.) Two days later laparotomy produced a large volume of similar fluid again sterile on culture. No cause for the peritonitis was apparent. The oedema then gradually disappeared and the albuminuria diminished to a trace. On discharge on September 14, and when he was seen again two months later, the urine still showed traces of albumin but no red blood cells were seen. His subsequent history is unknown. (He was a boarded-out child and all attempts to trace him have failed.)

Case A8. A girl aged 6 years was admitted on October 22, 1948. One week previously, on the day of her discharge from hospital after treatment for acute otitis media, her face became swollen and her urine was found to contain albumin. On re-admission she was found to have oedema of the face, back and legs; her blood pressure was 185/145 mm. Hg and the blood urea level 60 mg. %. The urine contained albumin+ but no red blood cells. Her blood pressure fell to 95/65 mm. Hg and the oedema disappeared completely one week after admission. Her urine was by then free from albumin and no red blood cells were ever seen on daily microscopic examination from the time of her admission. She was seen at intervals up to five and a half years from the onset of her illness and has remained well and free from any signs of renal damage (blood pressure, 120/80; routine urine examination and Addis count, normal).

Case A14. A boy aged 10 years was admitted on February 18, 1949. He had no history of recent infection. Four days before admission his face became swollen and he complained of abdominal pain. On admission he was breathless on moderate exertion and showed marked generalized oedema and a right pleural effusion. There was definite cardiac enlargement but no murmurs were heard; the neck veins were distended 1 in. above the manubrium and the liver edge was three fingerbreadths below the costal margin. His blood pressure was 140/100 mm. Hg, blood urea level 60 mg. %, and blood cholesterol level 288 mg. %. The urine contained albumin, 0·5 parts Esbach in a 24-hour specimen; no red blood cells were seen on microscopic examination. Signs of cardiac failure disappeared rapidly and after two weeks the oedema had gone and blood pressure had fallen to 120/85 mm. Hg. Traces of albumin persisted in the urine up to three weeks after admission, but daily microscopic examination showed very occasional red blood cells on three occasions only. When last seen six months later he was well, his blood pressure was 120/70 mm. Hg and his urine normal.

Case A37. A boy aged 1 year 4 months was admitted on November 3, 1950. There was no history of recent infection. Two weeks before admission he developed generalized oedema and passed dark urine. On admission he was generally oedematous; his blood pressure was 100/80 mm. Hg and blood urea level 70 mg. %. The urine contained albumin++ and scanty red blood cells. The oedema increased and he developed ascites, his maximum weight two weeks after admission being 34 lb. At this time the blood cholesterol level was 440 mg. % and there was still gross albuminuria, but red blood cells were usually absent on microscopic examination. Then oedema diminished gradually and had disappeared two months after admission when his weight was 22 lb. Albuminuria had also ceased. Two weeks later, accompanying an upper respiratory infection, albuminuria recurred but with virtual absence of even microscopic haematuria. Traces of albumin were still present when he was discharged three and a half months after admission. When last seen one and a half years after admission he was well, and urine examination showed no abnormality.

Group 3

Case 41. A girl aged 8 years was admitted on April 3, 1936. One month previously she developed a sore throat, followed one week later by a swelling of the eyelids. The oedema gradually spread, and on one occasion her urine was thought to have been dark. On admission she had marked oedema of the face and doubtful oedema elsewhere. Her blood pressure was 116/70 mm. Hg, blood urea level 30 mg. %, and blood cholesterol level 512 mg. %. The urine contained albumin++, and microscopic examination showed casts, pus cells and renal epithelium, but no red blood cells. During the first three weeks in hospital the oedema became gross and generalized and was accompanied by ascites and left pleural effusion. During the next three weeks the oedema gradually disappeared and albuminuria diminished. On 11 occasions microscopic examination showed no red blood cells in the urine. Two months after admission albuminuria had ceased, and when she was discharged one month later she had apparently made a complete recovery. She remained fairly well for one year but her parents noted that her

ankles were frequently swollen in the evening. She was then re-admitted with a 10 days' history of swelling of the face and legs, headache and the passage of scanty red urine. On admission her blood pressure was 110/78 mm. Hg, and her urine contained albumin++ and many red blood cells. For two and a half months oedema of varying degree persisted, her weight showing fluctuations between 73 and 85 lb. When the oedema was maximal her blood pressure rose and for over three weeks the diastolic pressure was between 92 and 104 mm. Hg. Microscopic haematuria persisted for 10 days after admission, then ceased and remained absent, though casts were consistently present. Albuminuria persisted and when she was discharged three months after admission, a 24-hour specimen contained 1 part Esbach. Over 10 years later she was very well, the urine was normal and the blood urea level was 37 mg. %. She was said to have recovered completely six months after her discharge from hospital and to have remained well ever since.

Case 117. A boy aged 7 years was admitted on April 10, 1941. Six days before admission he developed coryza and 24 hours later his face and legs began to swell. On admission he showed oedema of the face, legs and back. His blood pressure was 118/90 mm. Hg, and his blood urea level 30 mg. %. The urine contained albumin, 12 parts Esbach, and scanty red blood cells. On two occasions shortly after admission macroscopic haematuria was present and on three subsequent examinations red blood cells were seen microscopically; a considerable number of microscopic examinations thereafter showed casts only. Albuminuria fluctuated but was gross at the time of his discharge after 10 months in hospital. Oedema also varied considerably but was usually gross and generalized, with ascites; six weeks after admission, immediately following a plasma transfusion, he had a marked diuresis and his abdominal girth decreased by 8 in. in one week; two weeks later the oedema recurred and again became gross but had disappeared completely before his discharge. His blood pressure rose and remained elevated for three months after admission, the diastolic pressure usually being between 90 and 106 mm. Hg. The blood cholesterol level in the first two months was 840 and 713 mg. %, but had fallen to 160 mg. % before his discharge. The highest blood urea level recorded was 54 mg. %. Seven years later he was clinically well, his blood pressure was 130/70 mm. Hg and his urine was free from albumin and abnormal deposit.

Case 201. A boy aged 5 years was admitted on March 4, 1948. In December, 1947, he had a sore throat followed after two weeks by swelling of the face and ankles and obvious haematuria. He was kept in bed at home for four weeks, apparently recovered, and had been up and about for four weeks when the feet and legs again swelled up and red blood cells were found in the urine. On admission he showed oedema of the face and sacral region. His blood pressure was 100/70 mm. Hg and his blood urea level 19 mg. %. His urine contained albumin++, but no red blood cells were seen on microscopic examination. The oedema fluctuated considerably and was at times gross and generalized but had disappeared seven weeks after admission, when he was discharged to remain in bed at home. On July 26, 1948, he was re-admitted with gross generalized oedema which persisted till his discharge one month later. Throughout both periods in hospital albuminuria remained gross but repeated microscopic examination showed red blood cells on two occasions only. The blood cholesterol level varied between 624 and 928 mg. % and plasma proteins between 4·03 and 7·61 g. %, the lowest albumin/globulin ratio being 0·78/1. His blood pressure remained normal. He died at home in December, 1948.

Case A31. A girl aged 3 years was admitted on June 10, 1950. She had no history of infection after an attack of measles one year previously. Thereafter she never seemed really well, and three months before admission she developed generalized oedema. The urine is said to have been 'rather red' about this time. The oedema slowly disappeared before she was admitted on account of persistent albuminuria. On admission she appeared well and had no detectable oedema. Her blood pressure was 110/75 mm. Hg, blood urea level 16 mg. %, blood cholesterol level 245 mg. %, and plasma proteins 4·46 g. % with an albumin/globulin ratio of 1·41/1. The urine contained albumin, 4 parts Esbach, but no red blood cells. During four months in hospital the urine continued to show albumin++ but no red blood cells were ever seen. She was seen on three occasions up to two years from the time of her admission during which period she remained very well. Non-catheter specimens of urine showed faint traces of albumin on two of these examinations, but no abnormal deposit was ever present and an Addis count on her last visit showed only 100,000 red blood cells and no casts in a 12-hour specimen.

Case A32. A boy aged 7 years was admitted on June 12, 1950. Six weeks previously he developed 'croup', and two weeks later swelling of the face and ankles appeared. On admission he showed oedema of the face and legs. His blood pressure was 122/78 mm. Hg, his blood urea 28 mg. % and his plasma proteins 3·5 g. %. The urine contained albumin, 6 parts Esbach, and microscopic examination showed many casts but no red blood cells. During 14 months in hospital oedema varied considerably but was usually gross and generalized; he developed ascites, which required tapping on several occasions, and bilateral pleural effusions. The oedema ultimately disappeared after two short courses of A.C.T.H., each followed by a brisk diuresis which brought his weight from 81½ lb. to 61 lb. His blood pressure was elevated for a prolonged period, the highest reading being 138/102 mm. Hg, but had fallen to normal before his discharge. The blood urea level remained within normal limits, the blood cholesterol level varied between 300 and 830 mg. %, and the plasma proteins were never below 3·5 g. %, the

lowest albumin/globulin ratio recorded being 1·11/1. The urine showed heavy albuminuria throughout, the Esbach readings varying between 4 and 20 parts. Repeated microscopic examination in his first four months in hospital showed no red blood cells in the urinary deposit, but microscopic haematuria then began and persisted with brief intermissions throughout his stay in hospital: on several occasions the haematuria became macroscopic. An Addis count six months after admission showed: red blood cells 1,940,000, and casts 3,020,000, in a 12-hour specimen.

Slight oedema recurred for a time after his discharge from hospital, but when last seen three years after the onset of his illness he was outwardly well and active. He was free from oedema and his blood pressure was 110/75 mm. Hg, but the urine contained albumin++.

Case A36. A boy aged 3 years was admitted on October 31, 1950. His illness began insidiously three months before admission when he developed intermittent swellings of the face and limbs. The urine appeared dark and the output was low. On admission he showed oedema of the face, back and legs. His blood pressure was 120/90 mm. Hg, blood urea level 47 mg. %, and plasma proteins 5·25 g. % with an albumin/globulin ratio of 0·99/1. The urine contained albumin++ and microscopic examination showed no red blood cells. Throughout five weeks in hospital oedema varied and was at times generalized; his blood pressure fell to 112/78 mm. Hg; albumin was constantly in the urine, but red blood cells were found on only four out of 16 microscopic examinations. He remained in bed at home for one month after discharge and was then re-admitted with generalized oedema and gross haematuria. The oedema varied and the haematuria diminished slowly for six weeks. He then developed measles; 10 days later he showed less oedema but was otherwise unchanged. The urine contained albumin++ and scanty red blood cells. A course of A.C.T.H., 10 mg. six-hourly, was begun, and on the second day of this course a very profuse diuresis began and persisted until he became dehydrated: despite intravenous fluids he collapsed and died (nine months after the onset of his illness).

Necropsy showed some generalized dehydration, slight pulmonary oedema and pale wet kidneys of normal size. No other abnormality was demonstrated. The histological report on the kidneys was as follows:

'Nearly all the glomeruli showed some degree of sclerosis, although few, if any, appeared to be completely effete. This sclerosis was often associated with digitation of the glomerular tufts and numerous examples of adhesion between the tuft and the capsule were noted. Nevertheless, as a rule, the glomeruli were not unduly cellular; the glomerular capillaries were freely patent; epithelial crescent formation was only occasionally seen and there was no notable fibrous thickening of the capsules of Bowman. The tubular elements were comparatively healthy in appearance, apart from a minor degree of dilatation as an occasional feature; a moderate number of hyaline casts were present: deposits of pigment were often present in the loops of Henle and in a few convoluted tubules: the bulk of the pigment contained iron and little or no calcium (von Kossa). There was an appreciable but slight increase of the interstitial tissue discontinuously in the cortex associated with small foci of round cell infiltration. The mucosa of the renal pelvis was normal in appearance. The renal vasculature was normal.

'The renal lesion is an example of chronic glomerulonephritis. For the most part it seems to represent a late stage of Type 2 nephritis (Ellis), but it includes a few features which are more characteristic of the late stage of Type 1.'

Group 4

Case 17. A girl aged 2 years 11 months was admitted on January 19, 1935. One month before admission she developed a feverish cold and after an unspecified interval her body began to swell and her urinary output fell. On admission her breathing was distressed and she showed gross generalized oedema and ascites. Her blood urea was 24 mg. %, her urine was loaded with albumin, and, on microscopic examination, contained many casts and a few red blood cells. Subsequent examinations showed no red blood cells, but casts and pus cells persisted. Respiratory embarrassment persisted in spite of abdominal paracentesis. Her urinary output continued low, her general condition deteriorated, and she died nine days after admission.

At necropsy there was generalized oedema and ascites; the only other abnormality noted was in the kidneys. The left kidney was grossly enlarged and pale, the right kidney was small and contained several infarcts.

Histologically 'the kidneys showed marked tubular nephritis of a subacute variety. The tubules showed marked fatty infiltration and degeneration over the entire kidney on the left and over the upper part on the right. The glomeruli and interstitial tissues were practically normal.'

Case 115. A girl aged 3½ years was admitted on March 1, 1941. She had no history of recent infection. One week before admission oedema appeared, first in the face and later spreading to involve the entire body. She became drowsy, vomited at intervals, and complained of headache. On admission she was generally oedematous; her blood pressure was 104/84 mm. Hg and blood urea level 30 mg. %. The urine contained albumin, 13 parts Esbach, scanty red blood cells and many casts. She improved rapidly after admission and was discharged to rest at home after 17 days, the oedema having completely disappeared and the urine being practically free from albumin. She was re-admitted one month later with a recurrence of oedema, gross albuminuria, and scanty red blood cells in the urine. Her blood pressure was 116/90 mm. Hg and blood urea level 39 mg. %. The oedema increased steadily and her blood pressure rose to 120/100 mm. Hg. The blood cholesterol level was 710 mg. %. After a terminal episode of fever and diarrhoea she died four months after the onset of the illness. There was no necropsy.

Case 129. A boy aged 6 years was admitted on August 16, 1942. He had no history of recent infection. One week before admission his face began to swell and he vomited at intervals and complained of abdominal pain. On admission there was marked oedema of the face, back and legs. His blood pressure was 128/92 mm. Hg, and his blood urea level 52 mg. %. The urine contained albumin++ and a few red blood cells. For four months the oedema varied considerably and his blood pressure remained slightly raised. Albuminuria persisted, but the urine was usually free from red blood cells. He was discharged on December 28 to remain in bed at home. Oedema recurred intermittently till he was re-admitted on April 19, 1943, with gross generalized oedema. His blood pressure was then 115/80 mm. Hg and his urine contained albumin+++ but no red blood cells. During the next month he improved considerably and when he was discharged on May 26 he was free from oedema and the urine showed a trace only of albumin. Thereafter he had no further symptoms and when he was seen over five years later he was well and the urine was normal.

Case 145. A girl aged 10 years was admitted on March 13, 1944. She had no history of recent infection. One month previously her face began to swell, she became drowsy, complained of headache and vomited intermittently. On admission she showed oedema of the face and legs. Her blood pressure was 120/90 mm. Hg and blood urea level 23 mg. %. The urine contained albumin ++ but no red blood cells. She was discharged after six weeks almost free from oedema but with albumin still present in the urine. One month later she was re-admitted with moderate oedema of the face and legs. Her blood pressure was then 136/100 mm. Hg and the blood urea level 23 mg. %. The blood cholesterol level varied between 684 and 984 mg. %. She was discharged after three weeks, improved, but still with albuminuria. Repeated microscopic examination during both admissions had shown no red blood cells in the urine. Eight years later she was admitted to Aberdeen Maternity Hospital three months pregnant. She had slight oedema of the face and ankles; her blood pressure was 150/100 mm. Hg, blood urea level 20 mg. %, and blood cholesterol level 190 mg. %. The maximum specific gravity of the urine on a concentration test was 1,024. The urine contained albumin++ and an Addis count on a 12-hour specimen showed 230,000 red blood cells and 317,000 casts. She was kept at rest throughout the greater part of the pregnancy and delivered of a live child by Caesarean section four weeks from term. Her blood pressure had tended to rise and albuminuria had increased towards the end of pregnancy, but, on her discharge 18 days after delivery, her blood pressure had fallen to 130/100 mm. Hg and her albuminuria varied between 1 and 2·5 parts Esbach.

Case 161. A girl aged 1 year 4 months was admitted on January 8, 1945. Six weeks previously she developed a 'cold' and soon afterwards her face became swollen and her urine scanty and was found to contain albumin. On admission she showed gross generalized oedema. The blood urea level was 28 mg. % and the blood cholesterol level 320 mg. %. The urine contained albumin ++ and scanty red blood cells. No red blood cells were seen on further repeated urine examination; albuminuria and oedema steadily diminished and she was discharged after four weeks with normal urine. She has not been seen since, but in 1948 her mother reported that, after an apparent relapse lasting three weeks in April, 1945, she has remained well.

Case 176. A boy aged 6 years was admitted on January 21, 1946. Two weeks previously he developed a sore throat and a few days later his face began to swell. Oedema rapidly became generalized and he passed little urine. On admission he showed gross generalized oedema with ascites and bilateral pleural effusions. His blood pressure was 115/80 mm. Hg, blood urea level 27 mg. %, blood cholesterol level 306 mg. %, and plasma proteins 4·3 g. % with an albumin/globulin ratio of 0·45/1. The urine contained albumin++++ and very scanty red blood cells. For three months his condition was virtually unchanged except that the blood urea rose to 110 mg. %, then fell to 58 mg. %. The urine continued to show albumin ++++ but scanty red blood cells were present only occasionally. High-protein-low-salt diet, concentrated plasma transfusion, abdominal paracentesis, thyroid extract and 'neptal' all failed to produce any improvement in his general oedema. After three months he had a sudden spontaneous diuresis and in six days was completely free from oedema, which did not recur. Albuminuria to a lesser degree persisted until his transfer to Aberdeen City Hospital with chicken-pox on May 28. From there he was discharged home and was then seen as an out-patient at intervals until February, 1948. He remained very well and free from any symptoms, and the albuminuria rapidly diminished and ceased entirely by October, 1946. Thereafter his urine was normal on repeated examination. When last seen he was clinically well, his blood pressure was 110/80 mm. Hg, and his blood urea level 37 mg. %.

Case 199. A girl aged 1 year 2 months was admitted on February 6, 1948. Two weeks before admission she developed a 'cold' and one week later her face and legs began to swell. On admission she showed oedema of the face and legs and signs of bronchitis. Her blood pressure was 110/90. The Wassermann reaction was negative. The urine contained albumin++ and scanty red blood cells. The oedema rapidly became gross and generalized and then slowly disappeared: two weeks after admission the blood urea level was 32 mg. % and the blood cholesterol level 736 mg. %. She was discharged after 6 weeks free from oedema; the urine up to this time continued to show albumin++, but on only one occasion after the initial specimen were red blood cells present. She was seen again one year and almost four years after the onset of her symptoms, and on both occasions was clinically very well with normal urine.

Case A48. A girl aged 2 years was admitted on September 30, 1951. Three months before admission

she had a sore throat from which she never really recovered. One month before admission her legs began to swell; the swelling varied from day to day and gradually spread to involve the whole body. On admission she showed moderately severe generalized oedema. Her blood pressure was 120/70 mm. Hg and the blood urea level 24 mg. %. The urine contained albumin+++, scanty red blood cells and many casts. An Addis count on October 3 showed 228,000 red blood cells and 132,000 casts in a 12-hour specimen. Her weight slowly increased to 37 lb. one week after admission; during the next two weeks she had a moderate spontaneous diuresis and her weight fell to 30 lb., at which level she showed no obvious oedema. The urine continued to be loaded with albumin and an Addis count on October 17 showed 989,000 red blood cells and 556,000 casts in a 12-hour specimen. At this stage she developed measles and within one week of the onset albuminuria ceased and did not thereafter recur. During this time she was very well and her urine was repeatedly normal on routine examination. An Addis count on November 5 showed 64,000 red blood cells and 23,000 casts, and on November 14, 71,000 red blood cells and 5,900 casts. She was seen as an out-patient at intervals for over two years and remained very well, with normal blood pressure and urine. Four further Addis counts were well within normal limits.

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FIBROCYSTIC DISEASE OF THE PANCREAS IN THE NEWBORN

BY

ALBERT E. CLAIREAUX

From the Bernhard Baron Memorial Research Laboratories, Queen Charlotte's Maternity Hospital, and the Institute of Obstetrics and Gynaecology, University of London

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Fibrocystic disease of the pancreas in the newborn infant is usually recognized by the development of intestinal obstruction as a result of meconium ileus (Andersen, 1938). According to Bodian (1952), a certain number of infants affected by fibrocystic disease develop severe intestinal lesions during intrauterine life. The abnormal consistence of the mucus produced in the alimentary tract causes inspissation of meconium and leads to intestinal obstruction, perforation or even atresia of the bowel. In the older infant the disease is more likely to take the form of a severe nutritional disorder which is liable to be complicated by respiratory infection. In a number of patients the respiratory disorder may dominate the clinical picture (Farber, 1944). Intestinal obstruction is rare in this group of patients, but it has been reported by Levy (1951) and by Fisher (1954) as a late complication of fibrocystic disease.

On the other hand, a congenital disorder such as fibrocystic disease of the pancreas is liable to be undetected in the neonatal period unless it appears as meconium ileus. Bodian (1952) states that in his series no children died in the first days of life with fibrocystic disease other than those with meconium ileus. He was thus unable to compare the distribution of intestinal lesions in infants of this age group with and without meconium ileus. In this laboratory we have examined sections of the pancreas obtained from a consecutive series of 500 necropsies on newborn infants without finding a single example of fibrocystic disease.

Recently, however, a case was encountered of an infant who died from anoxia during delivery. At post-mortem examination severe fibrocystic disease of the pancreas was found and lesions were also visible in the liver. There was no evidence of intestinal obstruction and the large bowel was full of meconium. This appears to be the first recorded example of fibrocystic disease of the pancreas without an intestinal lesion in a newborn infant.

Case Report

The mother was a healthy woman aged 29 years and this was her second pregnancy. Her first pregnancy in 1953 resulted in the birth of a boy who is now alive and well. Delivery was effected by Caesarean section at 37 weeks on account of placenta praevia. She developed acute nephritis two months after delivery but recovered fully.

During the pregnancy she was quite well. She was Group O Rh positive and no antibodies were present in the serum. The haemoglobin was 12·7 g. % and red cells were 4·3 million per c.mm. A chest radiograph was normal and the Wassermann and Kahn tests were negative. Her blood pressure was 120/90 mm. Hg and no abnormal constituents were present in the urine. No abnormality was detected at routine ante-natal examination.

Labour began spontaneously on February 26, 1955, seven days after the estimated date of delivery. The patient's blood pressure had risen to 140/90 mm. Hg. The urine was still clear. The foetus presented by the vertex. A slight intrapartum haemorrhage occurred and signs of foetal distress became evident 12 hours after the onset of labour. The foetal heart rate fell to 80/min. and meconium was present in the liquor. On account of the foetal distress forceps delivery was carried out under local anaesthesia and when the cervix was fully dilated episiotomy was performed. The head was delivered slowly but the baby was now very limp and covered with meconium. The apex beat was not perceptible at delivery and all attempts at resuscitation failed. The placenta weighed 624 g. and was perfectly normal. The puerperium was uneventful.

Necropsy. The body was that of a well developed female infant weighing 2,975 g. No congenital abnormality was found on external examination.

The falx and tentorium were intact. The brain was firm and no lesion was found on slicing.

The larynx, trachea and bronchi were healthy. No free fluid was found in the pleural sacs. The lungs were intensely congested and subpleural petechial haemorrhages were present over their surface. There was evidence of aspiration of liquor amnii. The heart and great vessels were normal.

The peritoneum was healthy and no lesions were

present in stomach or bowel. The content of the small intestine was yellow and semi-fluid. There was no over-distension. The colon was loaded with meconium, which was rather yellow instead of the usual dark green. The consistence of the meconium was normal. The liver (140 g.) was large and congested. The capsule was smooth but numerous small white flecks were seen on the liver surface just beneath. Similar flecks were seen on the cut surface of the organ when sliced. The flecks were again near the capsule. The gall bladder was extremely small and narrow. It contained some yellow mucus. The bile ducts were patent.

The pancreas was firm and nodular. The surface was very irregular and on slicing greenish-white material could be expressed from the cut surface. This material looked like pus. No macrocysts were seen.

The spleen was small and firm. The lymph nodes were normal. The ovaries, tubes, uterus, thyroid, thymus, pituitary and suprarenal glands showed no abnormality.

Material expressed from the pancreas was examined bacteriologically. Smears showed numerous pus cells but no organisms. All cultures were sterile.

Histology. The pancreas showed a great increase in connective tissue with a marked atrophy of the acinar tissue. The degree of pathological change varied greatly from lobule to lobule. In some lobules the acini had almost completely disappeared and in these areas the gland was composed of enormously dilated ducts filled with amorphous, slightly eosinophil debris and polymorphonuclear leucocytes (Fig. 1). In some places the duct walls had undergone necrosis and pools of inspissated secretion had formed. The ducts were surrounded by dense fibrous tissue. It was presumably the material from these dilated ducts which was expressed when the pancreas was cut during post-mortem examination. Elsewhere the destructive process was less severe. The acinar tissue was still recognizable and in a very few areas appeared almost normal. The islets of Langerhans showed no change. Even in the less affected lobules, however, many acini were distended and filled with eosinophilic material which had the appearance of inspissated secretion (Fig. 2). The affected structures were surrounded by fibrous tissue which was infiltrated with lymphocytes and mononuclear cells. There was little evidence of necrosis in these areas, but again

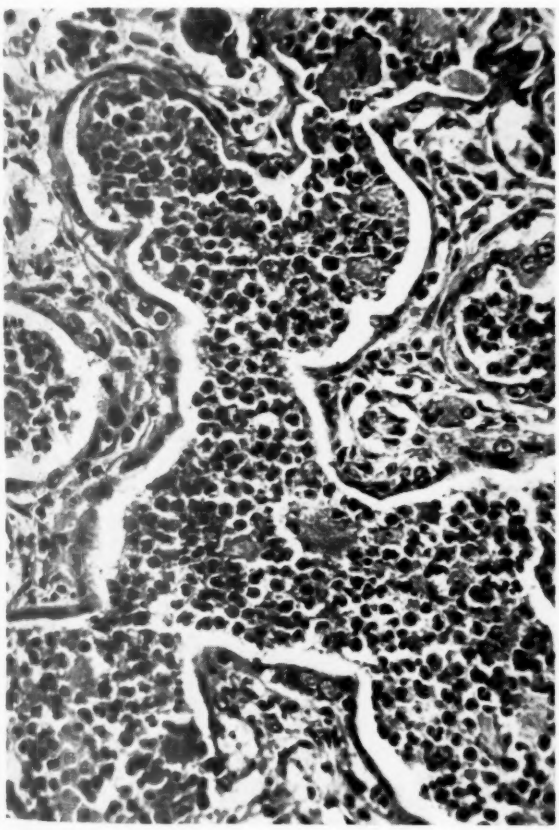

FIG. 1.—Pancreas ×250. Grossly distended pancreatic duct filled with acidophil debris and polymorphonuclear leucocytes. The smaller ducts are surrounded by proliferated fibrous tissue. (All sections stained with haematoxylin and eosin.)

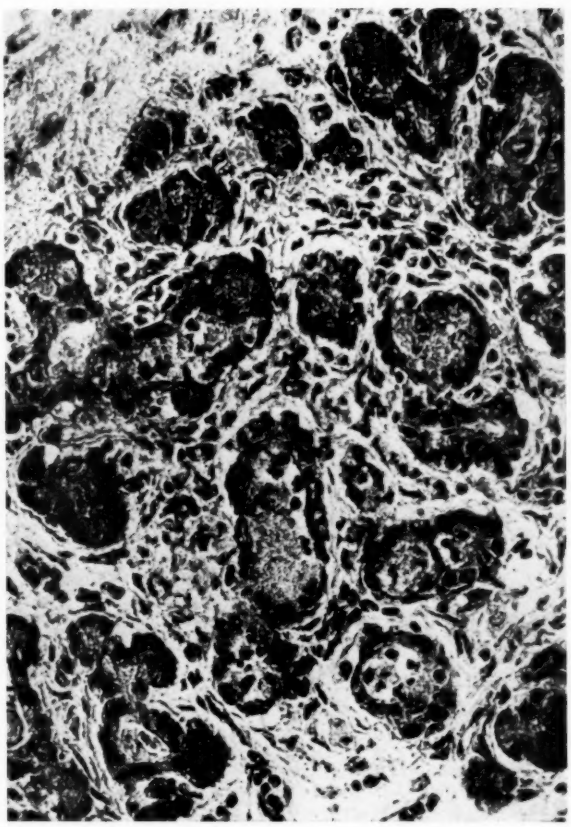

FIG. 2.—Pancreas ×250. Dilated acini filled with inspissated secretion. There is pronounced periacinar fibrosis but less evidence of inflammatory cell infiltration in this area.

infiltration with polymorphonuclear leucocytes was observed.

The liver showed focal biliary cirrhosis (Fig. 3). The portal tracts chiefly affected were those immediately beneath the capsule and corresponding to the white flecks observed on macroscopic examination. Elsewhere, especially toward the centre of the organ, the bile ducts and portal tracts had a normal appearance. In the cirrhotic areas there was proliferation of small bile ducts and an increase in the fibrous tissue stroma in the portal tracts. The bile ducts were distended and contained some amorphous material which stained brick-red with haematoxylin and eosin (Fig. 4). The material was probably inspissated mucus. The portal tracts were infiltrated with polymorphonuclear leucocytes and lymphocytes and mononuclear cells.

The lumen of the gall bladder was filled with thick mucus. The lining cells were of the tall columnar type. The wall was congested and fibrosed and no dilated mucous glands were seen.

The lungs were slightly expanded as a result of excessive aspiration of liquor amnii. Many alveoli and alveolar ducts contained cornified cells. The lungs were congested. The bronchi in the lung roots showed an abnormality of the mucous glands (Fig. 5). These glands were distended with inspissated secretion. The bronchial epithelium had a normal appearance.

The parotid gland appeared normal. The submandibular salivary glands showed moderate dilatation of groups of acini which contained mucus. The ducts contained mucous secretion. The changes were not severe. No sections were taken from the sublingual glands.

Sections were examined from the stomach, duodenum, ileum and colon. The gastric mucosa showed fairly severe post-mortem change. A few glands were distended with thick mucus, but they were the exception. Some of Brunner's glands in the duodenum were dilated and contained inspissated mucus, but the lesion was not pronounced. The ileum showed post-mortem change of the mucosa. A few dilated glands were present. The mucous membrane of the colon was healthy. The villi appeared normal. Many goblet cells contained mucus, but there was no glandular dilatation (Fig. 6).

The spleen, kidneys and suprarenal glands showed no pathological change.

Discussion

This infant obviously had severe fibrocystic disease of the pancreas. The criteria laid down by

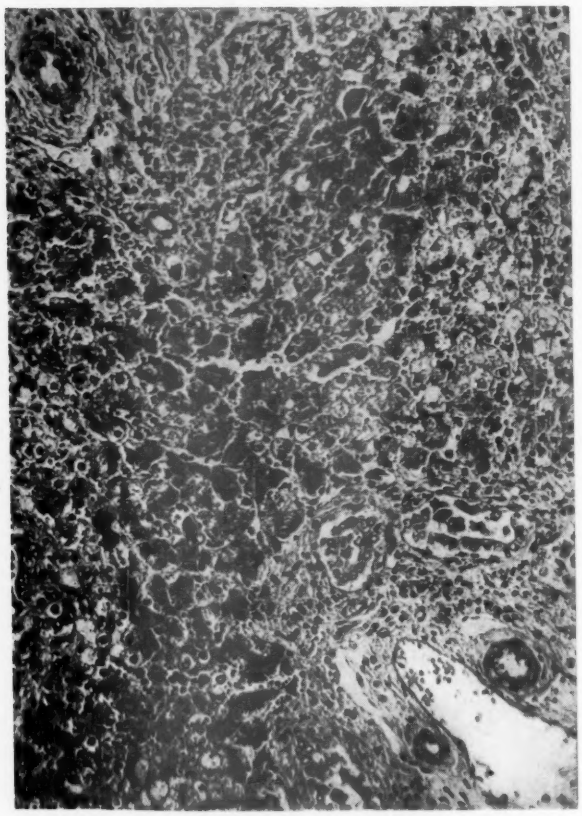

FIG. 3.—Liver ×100. Focal biliary cirrhosis. The portal tracts show proliferation of small bile ducts, increase in fibrous tissue and infiltration with inflammatory cells.

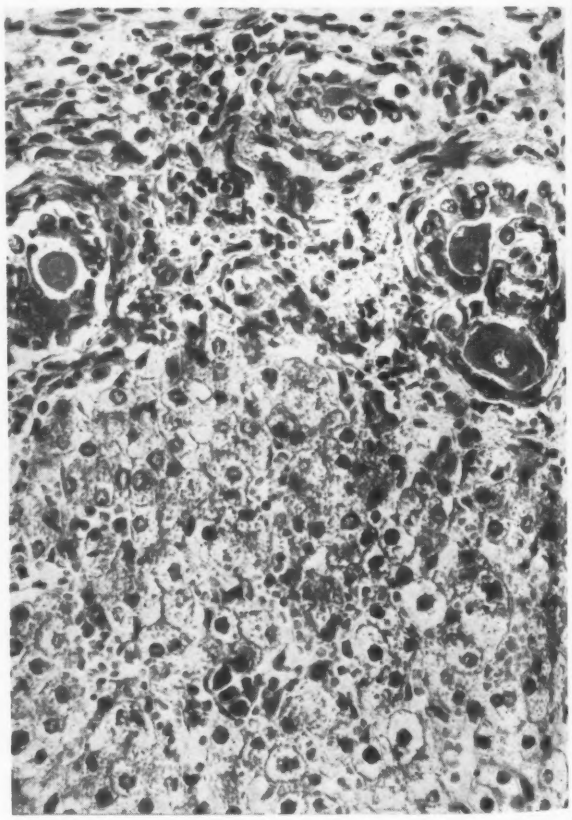

FIG. 4.—Liver ×250. Portal tract showing distended bile ducts containing acidophil secretion. There is an increase in fibrous tissue which is infiltrated with polymorphonuclear leucocytes and lymphocytes.

FIG. 5.—Lung ×100. Portion of wall of major bronchus showing dilatation of mucous gland which is packed with secretion. The gland on the right is emptying viscid mucus into the bronchial lumen.

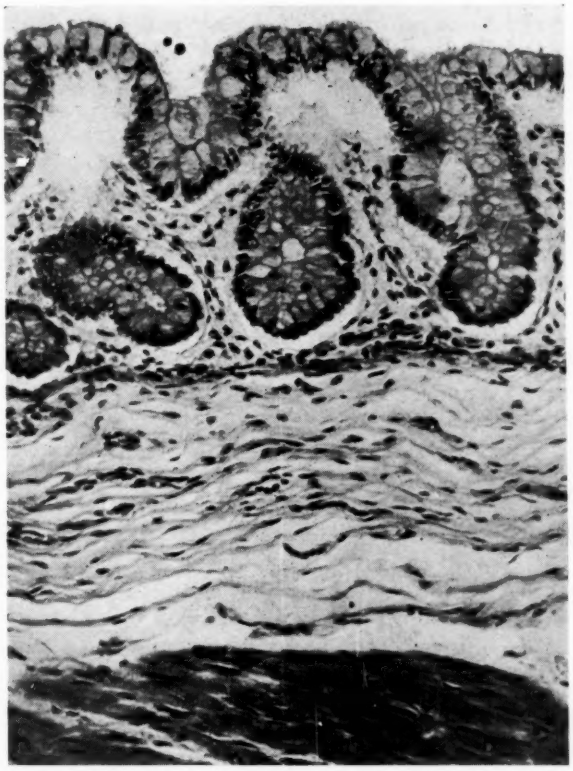

FIG. 6.—Colon ×150. Mucous membrane is healthy. Many of the goblet cells in the epithelium contain mucus, but there is no glandular dilatation.

Bodian (1952) were all present. There was an excessive quantity of abnormal secretion, atrophy of exocrine tissue and a fibroblastic reaction and fibrosis of the stroma. Some pancreatic lobules were much more severely affected than others and this is characteristic of the disease. In some areas there was almost complete fibrosis with disappearance of exocrine parenchyma and in others only mild dilatation of the acini was found. However, the pancreas in this case presented some rather unusual features. The lesion was very far advanced at this stage of development and the presence of such large numbers of polymorphonuclear leucocytes was most extraordinary. Farber (1944) found large mononuclear cells and evidence of lymphocytic infiltration in some of his material, but 'neither necrosis nor acute inflammatory changes were encountered'. Inflammatory infiltration was not a feature of the series reported by Bodian (1952). Both necrosis and severe inflammatory reaction occurred in this pancreas. The ducts were enormously distended with inspissated secretion and many were packed with polymorphs. The duct walls were also necrosed.

The cause of this inflammatory reaction is obscure. All attempts at recovering an organism failed. Bodian (1952) suggested that retained secretion may cause pressure atrophy of the exocrine tissue and during this process intracellular substances are liberated. These substances are believed to be irritant and produce a fibroblastic reaction and fibrosis. If such a process does occur it may explain the inflammatory changes in this case.

This question of inflammatory change is also connected with the development of the pancreatic lesion in its early stages. Farber (1944) found only inspissated material in the small ducts and acini, and no evidence of fibrosis in the early stage of fibrocystic disease. Di Sant' Agnese (1955), on the other hand, examined biopsy material from a patient suffering from fibrocystic disease. This patient still had normal pancreatic enzymes in his duodenal juice. In his case the pancreatic acini and islets were entirely normal, but there was an increase in fibrous tissue and an inflammatory reaction was present in the stroma. It is, of course, impossible to come to any conclusion on such slender evidence, but it may be that an inflammatory

reaction plays a greater part in the development of the early pancreatic lesion in some patients than has been suspected.

The pancreatic and other lesions in fibrocystic disease have hitherto been regarded as the result of abnormal mucus production, *i.e.*, mucosis. Recently, however, Di Sant' Agnese, Darling, Perera and Shea (1953) have shown that there is an increase in the quantity of electrolytes in the sweat of patients suffering from fibrocystic disease. The sweat glands show no histological change, but are said to be constantly affected in this condition. It would seem, therefore, that exocrine glands other than those producing mucus are affected and the exact pathogenesis of the histological lesions in the pancreas and elsewhere still awaits elucidation.

The liver and gall bladder showed typical changes. The gall bladder was small and fibrosed. It contained only thick mucus. The bile ducts were patent but narrow. No dilated glands were seen. The liver changes were striking. They were characteristically subcapsular in distribution and were very scanty in sections taken from the centre of the liver. They consisted of plugging of small bile ducts in the portal tracts with strongly acidophil secretion. There was proliferation of small bile ducts and a great increase in fibrous tissue in the affected portal tracts. The inspissated secretion had led to dilatation of these small ducts with resulting atrophy to the surrounding liver parenchyma, which had been replaced by fibrous tissue. The appearance was that of biliary cirrhosis which was predominantly focal in distribution. It is possible that this type of lesion plays a part in the development of liver cirrhosis reported by Webster and Williams (1953) in older children with fibrocystic disease. Inflammatory cell infiltration was also a feature of the lesions in the portal tracts and again the polymorphonuclear leucocyte played a prominent part. The density of the cellular infiltration in both the pancreas and the liver was quite exceptional.

The absence of any severe lesion in the intestinal tract was rather surprising. Occasional mucous glands in the stomach, duodenum and ileum were found and these were full of inspissated mucus. Most glands, however, were quite normal apart from rather severe post-mortem change. The colon was heavily loaded with light yellow meconium. This was probably the result of poor biliary secretion and no bile was seen in the gall bladder at necropsy. The consistence of the meconium seemed normal and some had passed through the anal sphincter into the liquor during delivery. This would seem to suggest that the development of meconium ileus is not only dependent on the presence of a severe pancreatic lesion, but also on the disorder of mucus production throughout the alimentary tract. This infant shows that severe pancreatic and liver changes can be present at birth in the absence of comparable lesions in the alimentary tract. Hitherto, cases of fibrocystic disease in the neonatal period have been associated with meconium ileus. In this condition the ileum is grossly distended above and is hypertrophied round inspissated meconium below. The colon is empty and is extremely narrow. By contrast in the present case the ileum was of normal calibre and the colon was full of soft meconium.

The changes in the salivary glands were slight. Unfortunately the sublingual salivary glands were not sectioned. As usual the parotid glands showed no change. The submandibular glands showed some retention of mucus secretion in the acini and the ducts were full of mucus. There was no atrophy of acinar tissue and no fibrosis.

In the respiratory tract the mucous glands of the major bronchi were dilated. The glands were filled with mucus but were not cystic. The changes were minimal and similar to those reported by Nash and Smith (1952). Their significance is doubtful.

There was no doubt that the infant died from the effects of anoxia just before delivery. The foetal heart rate had slowed to 80/min. just after intrapartum haemorrhage occurred. The infant passed meconium into the liquor and there was histological evidence in the lungs of excessive aspiration of liquor amnii. The intrapartum haemorrhage was probably the result of a premature separation of the placenta which was sufficient to interfere with the oxygenation of the infant.

It is interesting to speculate on the course of the disease if the infant had survived the hazards of delivery. The absence of alimentary tract lesions makes it unlikely that intestinal obstruction would have occurred during the neonatal period. The changes in the respiratory tract were very slight and would probably not have been sufficient to encourage the development of infection. The pancreatic lesions were severe and as they are progressive would have led to a very severe nutritional disturbance which would have been soon recognizable. The relationship between focal biliary cirrhosis in the newborn and the development of multilobular cirrhosis in the older child with fibrocystic disease is not yet known. It is possible that the latter condition is not solely the result of malnutrition and protein deficiency.

Summary

A case of fibrocystic disease of the pancreas in an infant who died during delivery is reported.

Typical lesions were present in the pancreas and liver. Mild changes were found in the submandibular salivary gland and in the mucous glands of the main bronchi and in some of the mucous glands of the alimentary tract.

There was no evidence of meconium ileus and the meconium was of normal consistence.

An unusual feature of the lesions in the pancreas was the intense inflammatory reaction. The inflammatory cells were mainly polymorphonuclear leucocytes. A brisk inflammatory reaction was also present in the portal tracts in the liver.

I am indebted to Professor J. McLure Browne for access to clinical records and to Mr. E. Clark of this laboratory for the photomicrographs.

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FIBROCYSTIC DISEASE OF THE PANCREAS PRESENTING WITH ACUTE SALT DEPLETION

BY

JOHN RENDLE-SHORT

From the Department of Child Health, the University, Sheffield

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During the hot summer of 1948, 10 patients were admitted to the Babies' Hospital in New York with heat prostration. No fewer than five of these children were cases of fibrocystic disease of the pancreas. Two further cases were discovered in subsequent summers. Reporting this interesting observation, Kessler and Andersen (1951) recorded that this special susceptibility to heat occurred in children who from the point of view of the fibrocystic disease seemed to be doing well; indeed, one child was thought to be normal and it was only in later investigations that he was found to have any underlying disease. Clinically the cases presented with vomiting, pyrexia and dehydration. Two children perspired freely, and in the two cases in which the observation was made low plasma chlorides were found on admission, namely, 59 and 81 mEq./litre (335 and 526 mg. per 100 ml.).

Stimulated by this work, Di Sant'Agnese, Darling, Perera and Shea (1953) measured the quantity and electrolyte composition of the sweat in cases of fibrocystic disease. No difference in the volume of sweat was noted between the children with the disease and controls and great individual variations were observed in both groups. The electrolyte content of the sweat, however, was significantly higher in children with fibrocystic disease (Table 1).

Di Sant'Agnese and his colleagues gave details of a further six cases of heat prostration in children with fibrocystic disease occurring in the summer of 1952. It is notable that the ages of these children ranged from 3 to 13 years; four of them had little respiratory involvement and the other two had only mild pulmonary disease.

TABLE 1

ELECTROLYTE CONTENT OF SWEAT IN 43 PATIENTS WITH FIBROCYSTIC DISEASE AND 50 CONTROLS*

	Electrolyte Content of Sweat (mEq. per litre)				
	Chloride		Sodium		Potassium
	Range	Mean	Range	Mean	Mean
Fibrocystic disease	60–160	106	80–190	133	18
Controls	4– 80	32	10–120	59	12

* Figures taken from Di Sant'Agnese *et al.* (1953).

No case of heat prostration associated with fibrocystic disease of the pancreas has yet been described in Great Britain, presumably for climatic reasons. Nor have any cases been recorded in this country or abroad of the disease presenting with salt depletion in the absence of excessive heat. The following case record is therefore of interest.

Case Record

Kenneth weighed 6 lb. 12 oz. at birth. His father suffers from diabetes mellitus, but his mother and three siblings are healthy. Kenneth was successfully breast fed and appeared to be perfectly well until three weeks before his admission to hospital in October, 1954, at the age of 3 months. He then started to cough and his respirations became laboured and grunting, but at that time no abnormal physical signs could be found. During the next few days he had bouts of crying, between which he was quite cheerful and smiling. He sweated considerably and his mother subsequently remarked that he 'tasted salt'. Although there was a fire in his room his parents state that he was not covered by an excessive number of bed-clothes. His motions were small and green and his urine became scanty: two days before admission he was dry for 21 hours. Throughout the illness he continued to feed well at the breast and only vomited on one occasion after he had been given oral penicillin. He was seen several times by his family doctor and given intramuscular penicillin, but no abnormal physical signs could be found. The night before admission the child suddenly went limp and blue. His breathing appeared to stop and his eyes turned upwards. After about 10 minutes he rallied and sucked at the breast. He was then sent into hospital. On admission he was found to be an ill, grossly dehydrated baby with pink lips. His respiration rate was 38 per minute and nothing abnormal was found in the chest, heart, abdomen, ears or urine. A chest radiograph was normal. At first sight the most probable diagnosis seemed to be gastro-enteritis, but he was a breast-fed baby and a stool passed

while he was being examined was small, emerald green and of normal consistency. Diabetes mellitus was also considered in view of the family history, but the normal character of respirations made this improbable; there had been no polyuria and his blood sugar was 135 mg. %.

The possibility of an Addisonian crisis and adrenogenital syndrome was considered, although the genitalia were normal and the family history was negative. Biochemical investigations were performed with the following results:

Plasma chloride (as NaCl), 365 mg./100 ml. (62·0 mEq./litre); plasma bicarbonate, 80 vol./100 ml. (36·0 mEq./litre); plasma sodium, 280 mg./100 ml. (122 mEq./litre); plasma potassium, 16·2 mg./100 ml. (4·6 mEq./litre).

The diagnosis of an Addisonian crisis was finally abandoned when, after a period of anuria, a specimen of urine was obtained and was found to contain no chloride.

Symptomatic treatment for the dehydration and salt loss was instituted, the child being given normal saline intravenously and desoxycorticosterone acetate (D.O.C.A.) and cortisone intramuscularly. Each specimen of urine was tested for chlorides and daily plasma chlorides estimations were performed. These levels both rose satisfactorily and the plasma bicarbonate fell to normal. Four days after the start of therapy the biochemical changes had been somewhat overcorrected; the urinary chlorides were now 808 mg./100 ml. (137 mEq./litre) and the plasma potassium had risen to 26·0 mg./100 ml. (6·6 mEq./litre). The 17-ketosteroids were 0·2 mg. per day and the 17-ketogenic-steroids 2·5 mg. per day, figures which are within normal limits.

When the child's biochemical upset had eventually been corrected his general condition was excellent. He was discharged home still breast feeding, but requiring a small complement.

At that time no cause for the dehydration was discovered. It was assumed that he had had an illness during which he sweated excessively and lost a large quantity of water and sodium chloride. The electrolyte content of his mother's breast milk was measured while she was in hospital with the following results:

Chloride, 74 mg./100 ml. (12·6 mEq./litre); sodium, 13 mg./100 ml. (5·9 mEq./litre); potassium, 53 mg./100 ml. (13·6 mEq./litre).

After discharge the child was not seen at the hospital for nine months as the family live some distance away, but the family doctor, Dr. Mainman, kindly informed us of his condition during this time. He reported that the only complaint by his mother was of offensive smelling stools. This symptom persisted and four months later the child developed a respiratory infection which proved very resistant to treatment. A radiograph of the chest then showed generalized hyperaemia most evident at the lung bases and consistent with a recent infection. During this time he developed a right inguinal hernia for which he was again referred to hospital.

The history of an intractable respiratory infection and foul-smelling stools coupled with the previous episode of acute dehydration immediately suggested the diagnosis of fibrocystic disease of the pancreas and efforts were made to confirm this.

Clinically the child looked well; his weight at 1 year was 22 lb. There were no abnormal physical signs apart from a reducible right inguinal hernia. His stools were very foul and his mother stated that fat oozed from the anus, but we were unable to confirm this.

Specimens of duodenal juice and stool both showed tryptic activity up to a dilution of 1 in 5 only. No iodine was detectable in the urine up to 24 hours after ingestion of 5 ml. iodized poppy seed oil B.P. (Silverman and Shirkey, 1955). A fat balance on a 37 g. per day fat intake showed that the child absorbed 84% of fat. A radiograph of the chest showed patchy collapse and emphysema. Analysis of saliva and sweat (obtained by the method of Shwachman, Leubner and Catzel, 1955) gave the following results:

Saliva	Sodium	48 mEq. per litre (110 mg./100 ml.)
	Chloride	45 mEq. per litre (263 mg./100 ml.)
Sweat	Sodium	122 mEq. per litre (279 mg./100 ml.)
	Chloride	106 mEq. per litre (263 mg./100 ml.)

These results are consistent with those obtained in fibrocystic disease of the pancreas by Di Sant'Agnese *et al.* (1953).

Discussion

During Kenneth's first hospital admission his stools were reported as normal apart from a single occasion just before his discharge. At this time he was receiving breast milk with a small complement of National dried milk. His mother weaned him off the breast soon after he returned home, the stools then becoming very offensive. It is possible that the innocuous nature of the stools in hospital may have been due to the fact that he was breast fed, the alimentary involvement only becoming manifest when he was weaned. On the other hand, as has been shown by Di Sant'Agnese (1955), pancreatic involvement is not essential for the diagnosis of fibrocystic disease, and perhaps the child's pancreas was not severely damaged by the age of 3 months.

The main interest in this case lies in the fact that the patient developed acute salt depletion from excessive sweating due, not to heat, but to some unknown illness. This was probably a respiratory infection, but it could have been paroxysmal tachycardia or some other condition. Acute salt depletion is therefore a danger to which children with fibrocystic disease are exposed whenever they have an illness in which they perspire freely. Extra salt should be given at these times. Conversely, it is obvious that any child with heat prostration or unaccountable dehydration should be investigated for possible underlying fibrocystic disease of the pancreas.

Summary

A case of fibrocystic disease presenting with dehydration and salt depletion is recorded.

The water and salt loss was due to excessive sweating occasioned not by heat, but by an illness, probably a respiratory infection.

My thanks are due to Dr. A. Livingstone and Dr. E. R. Mainman, who referred this child to us and who kept us informed of his progress, to Miss E. Finch who performed the biochemical investigations and to Professor R. S. Illingworth for his helpful criticism.

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A CHEMICAL STUDY OF MUCIN IN FIBROCYSTIC DISEASE OF THE PANCREAS

BY

CHARLOTTE ANDERSON and MAVIS FREEMAN

From the Clinical Research Unit, Royal Children's Hospital, Melbourne, Australia

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The aetiology of the condition fibrocystic disease of the pancreas is still unknown, but it is considered likely that the pathological changes are brought about because the mucus produced is more viscid than normal.

Farber, Shwachman and Maddock (1943) were the first to observe that the fluid obtained from the duodenum of cases of fibrocystic disease of the pancreas was scanty and viscid, and said that the gross appearance of the material had its counterpart in the histological appearance of inspissated material in the acini and ducts of the pancreas. They also found that the mucous glands throughout the respiratory and alimentary tracts were distended and filled with inspissated material similar to that of the pancreas. On this evidence they postulated that an altered secretion from the mucous glands was the basis of this disorder. Two possible causes for this alteration were suggested: first, deficiency of mucus, and secondly, excess of vagal activity, the latter being due to autonomic imbalance in the control of mucous gland secretions. No further evidence was produced to support these theories.

Bodian (1952), in his survey of cases purely from the clinical and histological point of view, conceived of the disease as a 'mucosis', or a congenital disorder of mucus production. Shwachman, Leubner and Catzel (1955) measured the viscosity of duodenal fluid obtained by intubation from cases of this disease and found that the fluid was more viscous than fluid from subjects with normal pancreatic function.

Apart from these observations which have been confirmed by others, there has been no evidence recorded to show that the mucin produced by mucus-secreting glands in these cases is any different from that produced by normal subjects. No chemical studies of the mucin in this disease have been reported. Buchanan and Rapoport (1952) made a chemical comparison of normal meconium and meconium from patients with meconium ileus, and decided that the main components of normal meconium were mucopolysaccharides. They found that meconium from a patient with meconium ileus contained less carbohydrate and more nitrogen and that it behaved like a protein in its precipitation reactions. They thought that the persistence of protein in the meconium of an infant with meconium ileus was probably accounted for by the lack of tryptic enzyme secretion into the intestine. The abnormally high viscosity of the abnormal meconium might then be attributed to the fact that frequently mucoproteins exhibit higher viscosities than mucopolysaccharides.

The present study was carried out to see if any difference could be found in the chemical components of mucus from cases of fibrocystic disease of the pancreas and subjects with normal pancreatic function. The study of mucus obtained from the human subject with this disease is beset by the difficulty of obtaining specimens in sufficient quantity and relatively uninfected by organisms.

Material and Methods

Gastric mucus obtained from post-mortem material was chosen as the only easily available source of material, and also because there had been chemical studies of mucus obtained from this source (Aminoff, Morgan and Watkins, 1950).

The qualitative difference between gastric mucus from eight young children dying with fibrocystic disease of the pancreas and a series of eight young children dying from other disease not involving the pancreas was studied. The mucus was removed from the stomach as soon as possible after death, the stomach being refrigerated until handled.

The fractionation procedure of Smith (1950) for hog gastric mucin was followed. The mucosae were too thin to be separated from the muscle wall by dissection, but the mucous surface was well scraped until all the available mucus was separated. The weight of this material was noted. After the addition of hydrochloric acid it was allowed to autolyse in the presence of toluene at 37° C. for five days. After filtration and adjustment to *p*H 4,

the mucoid material was separated by precipitation with 5 volumes of cold ethyl alcohol. The precipitate was collected by centrifuging, dissolved in water, and dialysed in cellophane in the cold against daily changes of distilled water for five days. The contents of the dialysis bag was centrifuged to separate out any insoluble material. This was washed, dried and weighed. The solution remaining was again precipitated by alcohol, centrifuged, dried and weighed. Any material in the dialysate was recovered after evaporation of the water on a boiling water-bath and precipitation by alcohol. There were only traces of insoluble and dialysable fractions. The soluble mucin was 0·5% by weight of the wet mucus removed from the stomach.

In order to determine whether the two pooled purified samples of mucin were identical, an analysis was made of nitrogen content, reducing power and of glucosamine content as was done by Aminoff *et al.* (1950) on human mucoid substance. The nitrogen estimations were made by the micro-Kjeldahl method. After hydrolysis with 0·5 N hydrochloric acid at 100° for 16 hours, the reducing power was estimated by the micro-Somogyi (1937) method, and glucosamine by the method of Elson and Morgan (1933). The data obtained are shown in Tables 1 and 2. These results are in the range found for partially purified mucin by the earlier workers quoted. It is apparent that the material obtained from cases of fibrocystic disease of the pancreas is the same as that found in other subjects, as far as the estimations made are concerned. The percentage of purified mucin in the wet mucus is the same, and the percentages of nitrogen and reducing power as glucose and glucosamine are almost identical in the two series.

Analysis of the insoluble fractions from both series show the presence of other substances, not mucoid, as impurities. Their reducing power is only of the order of 5 to 6% and their nitrogen content 7 to 8%. Some of this matter is bacterial in origin as complete filtration by paper is impossible.

TABLE 1

GASTRIC MUCUS FROM CASES OF FIBROCYSTIC DISEASE OF PANCREAS AND CONTROLS

	Controls	Fibrocystic Disease of Pancreas
Number of cases	8	8
Average weight of wet mucus (g.)	4·3	8·7
Average weight of purified mucin (mg.)	23·1 (range 2·2–48·0)	45·9 (range 16·7–72·4)
Purified mucin in wet mucus (%)	0·54	0·52

TABLE 2

CHEMICAL COMPOSITION OF POOLED SPECIMENS OF STOMACH MUCIN FROM CASES OF FIBROCYSTIC DISEASE OF PANCREAS AND CONTROLS

	Controls	Fibrocystic Disease of Pancreas
% Nitrogen	6·82	6·54
% Reducing power as glucose	36·3	35·3
% Glucosamine	21·5	22·5

Summary

From the observations of earlier workers it seems likely that in fibrocystic disease of the pancreas there is a difference in the mucus produced in the body. However, at present the evidence rests on histological observations and observation of the physical property of viscosity. The present study indicates that there is no difference with regard to properties as a mucoprotein between mucin obtained from the stomach in children with fibrocystic disease of the pancreas and that of children with normal pancreatic function. The ratio of nitrogen content to reducing power is of the same order. The quantity of mucin in wet mucus also appears similar.

Is it possible that variations in the polymerization of the mucus may be responsible for the differences observed in physical properties?

Our thanks are due to the Pathology Department of the Royal Children's Hospital for cooperation in the collection of material.

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THE HYALINE MEMBRANE SYNDROME IN PREMATURE INFANTS

BY

WILLIAM BLYSTAD

From the Children's Department, Rikshospitalet, Oslo

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In recent years attention has been drawn to the frequent occurrence in premature infants of a characteristic clinical picture of dyspnoea setting in a few hours after birth. This condition, which is also observed in full-term infants, will be called here 'early neonatal dyspnoea'. Investigations in full-term infants presenting this clinical picture have produced evidence of an increased minute volume and considerably increased respiratory effort (Karlberg, 1954). Blood gas analyses carried out on premature infants presenting the same picture have shown, notwithstanding increased respiratory effort, marked respiratory failure, which must be of pulmonary origin and causes a pronounced acidaemia, and seems to be the principal cause of death in the fatal cases (Blystad, 1955). It has been held that this clinical picture bears a relationship to the development of hyaline membrane and atelectases in the lungs, 'the hyaline membrane syndrome' (Parmelee, 1952; Miller and Behrle, 1953; Clifford, 1953; Arey and Dent, 1953; Potter, 1952, 1953; M. & R. Dietetic Laboratories, 1953).

The object of the present research was to test this hypothetical aetiological relationship.

Materials

The study is based on a clinical and pathological study of 47 premature infants who died in the course of the early neonatal period. Post-mortem examinations were carried out in the pathological laboratory of the hospital.

Results

According to the clinical picture the material has been classified into two groups. The first of these groups includes 25 premature infants presenting the typical clinical picture of early neonatal dyspnoea; 11 of these patients also had one or more attacks of apnoea, and in four the dyspnoea gradually changed into a protracted stage of respiratory depression, lasting several hours, before death. All the patients in this group died within the first four days of life.

The second group comprises 22 patients who showed no sign of early neonatal dyspnoea. Instead, respiration, which was slow and gasping, was depressed, and in 18 there were protracted attacks of apnoea. Death occurred in the course of the first five days of life.

Convulsions or a bulging fontanelle, indicating a severe intracranial haemorrhage, were observed in none of the 47 cases.

Tables 1 and 2 show the pulmonary and intracranial findings revealed by the necropsy. The patients in the first group showed marked pulmonary changes, and extensive atelectases were seen in all the cases. Hyaline membrane was found

TABLE 1

PULMONARY NECROPSY FINDINGS IN 47 PREMATURE INFANTS DYING IN THE EARLY NEONATAL PERIOD

Pulmonary Findings	Early Neonatal Dyspnoea	Respiratory Depression
Atelectasis and hyaline membrane	9	7
Atelectasis and hyaline membrane and pneumonia	6	—
Atelectasis and pneumonia	1	3
Atelectasis and haemorrhage	2	2
Atelectasis and hydrothorax	1	—
Atelectasis alone	6	10 (5 light)
Total	25	22

TABLE 2

INTRACRANIAL PATHOLOGICAL FINDINGS IN 47 PREMATURE INFANTS DYING IN EARLY NEONATAL PERIOD AFTER MARKED RESPIRATORY COMPLICATIONS

Intracranial Findings	Early Neonatal Dyspnoea	Respiratory Depression
Subdural haemorrhage	3	8
Subarachnoid haemorrhage	2	2
Intraventricular haemorrhage	—	1
Intracerebral haemorrhage	2	—
No haemorrhage	17	9
Not examined	1	2
Total	25	22

in 15 of the 25 infants. In four cases there was a relatively severe pneumonia, and in the three others the pneumonic foci were few and scattered. In this group the intracranial haemorrhage in four of seven cases seemed to have been moderate.

In the second group obvious abnormal pulmonary findings were also noted in most cases. In five cases, however, the only finding was a fairly moderate atelectasis. Seven of the 22 patients had hyaline membrane in the lungs. Intracranial haemorrhage was somewhat more frequent in this group, which in several cases was more extensive than in the first group.

Discussion

In 15 of the first group of 25 infants presenting with early neonatal dyspnoea necropsy revealed hyaline membrane and pulmonary atelectasis. In the remaining 10 cases presenting with the same clinical picture, hyaline membrane was absent but there were significant pulmonary changes in the form of marked atelectasis, pneumonia or haemorrhage. These findings suggest that though the clinical picture of early neonatal dyspnoea indicates the presence of marked pulmonary changes it does not give certain information as to their nature. Most frequently, however, massive atelectasis will dominate the picture. The cause of the atelectasis and the significance of the hyaline membrane are not yet clear.

In the second group of 22 premature infants the clinical picture was characterized by a depressed respiration which might seem to indicate a damaged central nervous system. Nevertheless, in seven of these patients the necropsy revealed hyaline membrane and atelectasis. Thus, these pathological changes are often present also in cases where no dyspnoea has been observed. Significant pulmonary findings in the form of atelectasis, pneumonia or haemorrhage were also seen in many of the other patients of the second group. An evaluation of the significance of the pulmonary findings will be difficult. It is possible that they are mainly secondary to a central injury with depression of the respiration and asphyxia. Intracranial haemorrhage was relatively frequent in this group. However, in nine cases there was no haemorrhage, and the origin of the respiratory depression will have to be sought elsewhere.

The absence of dyspnoea does not, of course, exclude the possibility that the pulmonary changes were the primary cause of the asphyxia in some of the infants of the second group also. The poorly functioning lungs could have led to anoxic depression of the respiratory centre, which could then no longer respond adequately to the respiratory situation. Such a development was easily discernible in several of the first group of infants with early neonatal dyspnoea, in whom, after an initial stage of increased respiratory effort, the picture changed into a relatively protracted phase characterized by markedly depressed respiration. I believe that in many premature infants pulmonary pathological changes constitute the main cause of asphyxia even where no early neonatal dyspnoea has been observed.

Summary

The clinical data and the necropsy findings of 47 premature infants who died in the course of the early neonatal period were examined. Early neonatal dyspnoea was observed in 25 patients. In all cases there was extensive atelectasis. In 15 of these the necropsy revealed hyaline membrane in the lungs. The other patients with this clinical picture also showed marked pulmonary changes. The clinical picture reflected a pulmonary pathology of varying character, in which marked atelectasis of unknown origin was a constant finding.

In 22 patients respiration was depressed centrally. In these intracranial haemorrhage was found somewhat oftener but was not a precondition to the establishment of this clinical picture. In this group considerable pathological changes were also frequently found in the lungs. In seven cases the necropsy revealed hyaline membrane. It is probable, in spite of the lacking dyspnoea, that pulmonary changes were the main cause of the asphyxia in some of the patients in the second group.

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A NEW TECHNIQUE FOR BRONCHOGRAPHY IN CHILDREN

BY

JOHN B. BROOKS and JOSEPH W. LEWIS

From Harefield Hospital, Harefield, Middlesex

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Bronchography in children has its own particular problems. Because the diameters of the bronchi are smaller than those in adults the viscosity factor of the contrast medium is relatively more important. The use of a too viscous medium in outlining the bronchial tree may lead to respiratory embarrassment. Bronchial secretion in bronchitic and bronchiectatic cases is also more likely to interfere with the obtaining of a good picture. It is, therefore, important that proper postural drainage be carried out beforehand.

Any method employed must be almost or entirely painless and must, if necessary, be independent of the child's cooperation. It might be thought that bronchography in an anaesthetized child would yield the best results. However, experience with several techniques has shown us that failure to obtain satisfactory bronchograms is frequently due to alveolar flooding. This may be due to hyperpnoea or to controlled or assisted respiration using relaxants.

After using other methods over a considerable period with variable success, we have evolved the method described below. It has been used successfully in 40 cases of which more than half had gross bronchiectasis and considerable bronchial secretion. These cases are the ones in which really satisfactory bronchograms are difficult to obtain. Our particular aim was not to exclude the presence of gross bronchiectasis (which is easily achieved by almost any method), but to get complete and optimal filling of the whole bronchial tree, resulting in bronchograms good enough for decision for or against operation. The age range of the cases dealt with was from 3 to 17 years, but most were between 4 and 10.

Materials

The following are required:

(1) Anaesthetic apparatus for the administration of nitrous oxide and oxygen.

(2) A 10-ml. syringe containing 10 ml. of 5% thiopentone.

(3) A 2-ml. syringe fitted with a No. 12 needle containing 2 ml. of 4% 'xylocaine' (lignocaine hydrochloride) for crico-thyroid or tracheal injection.

(4) A spray containing 4 ml. of 4% 'xylocaine'.

(5) A 2-ml. syringe containing 2 ml. of 'scoline' (succinyldicholine chloride) for occasional use.

(6) A No. 1 Magill nasal tube with a small safety-pin stuck through it so that when introduced into the nose as far as the pin its tip is midway between the cords and carina. The pin is also useful in helping to secure the tube to the face with strapping.

(7) A 2-ft. length of No. 4 polythene tubing marked with a small piece of strapping so that when threaded through the Magill tube it projects a quarter to half an inch beyond its end.

(8) Suction apparatus and No. 8 gum elastic catheter for aspiration as necessary through the Magill tube.

(9) A bronchoscopy trolley and child's laryngoscope available for immediate use.

(10) A 20-ml. syringe containing the contrast medium and fitted with a thick needle of suitable diameter to fit tightly into the polythene tubing.

Preliminary Treatment

Clinical examination will indicate the necessity or otherwise for breathing exercises. If there is secretion, as is frequently the case with bronchitis and bronchiectasis, postural drainage should be carried out regularly. It is particularly important to carry out posturing an hour or two before the actual bronchography as this may make all the difference between a good and a bad bronchogram. In cases where there is much sputum, the responsible organism should be tested for sensitivity and treatment by the appropriate antibiotic instituted. In this connexion we have frequently encountered cases which have been ineffectually treated previously with small doses of antibiotics. A further 10-day course entailing large doses of the order of 1 mega unit twice daily when crystalline penicillin is used had led to marked improvement in many of these cases. When there is no sputum we nevertheless cover the actual bronchography with a five-day routine course of penicillin, since we have found that it reduces the likelihood of systemic disturbance after bronchography. The child should have no food or drink on the morning of bronchography, and it is therefore better for the investigation to be carried out

early in the day to avoid unnecessary distress. The premedication was 'omnopon' (grain 1/24 per stone body weight) with hyperduric atropine, grain 1/100. Administration of this at the correct time is important. If the child is old enough and intelligent we usually explain beforehand what we are about to do, as we find that we get better cooperation at the time of the bronchography.

Anaesthesia and Procedure

The child is anaesthetized with a sleeping dose of thiopentone of the order of 0·1 g. in a 4-year-old, and 0·2 g. in a 7-year-old. If an injection is resented, anaesthesia is induced with nitrous oxide and oxygen and the thiopentone given when the child is asleep.

Two millilitres of 4% 'xylocaine' is now injected either through the crico-thyroid membrane or the trachea itself; the child coughs and spreads the local anaesthetic widely in the trachea and over the larynx. The anaesthetic facepiece is now applied and a mixture of nitrous oxide, oxygen and carbon dioxide given until the child is hyperventilating. While the child inspires deeply, 4% 'xylocaine' is sprayed up the nostril through which it is proposed to pass the Magill tube. This results in good anaesthesia of the nose and pharynx. The facepiece is reapplied and the same mixture of gas is given. The Magill tube is then passed blindly as the child hyperventilates. In cases of difficulty, the tube can be passed under direct vision, following a small dose of 'scoline'.

At this stage, if secretion is audible through the Magill tube, the gum elastic catheter is pushed down it and the trachea and bronchi aspirated. The catheter is removed, the polythene tube is passed down the Magill tube as far as its mark, and 2 ml. of 'xylocaine' injected through it into the lower end of the trachea. The polythene tube is removed and with suitable posturing the solution anaesthetizes the bronchial tree on the side under investigation. Following this, aspiration of secretion or excess anaesthetic solution through the gum elastic catheter is sometimes needed.

In a few minutes the child wakes and as he feels no discomfort with the Magill tube in his nose he is easily reassured. He is taken into the *x*-ray room and the polythene tube is connected to the syringe containing the contrast medium and filled to its end. It is then pushed down the Magill tube as far as its mark. The child is postured to outline each bronchus in turn. For children below the age of 14 we use from 8 to 14 ml. of oily 'dionosil' 60% w/v, and this is distributed equally throughout the lobes. A proportion of the 'dionosil' is injected for each change of posture. The bronchi are filled in the following order: the basals, the dorsal, the middle on the right, and lastly, the upper lobe bronchi including the lingula if the left lung is being investigated.

The polythene tube is then removed and the radiograph taken. The whole procedure can be done without haste, an important factor in obtaining good quality bronchograms. The child is not connected to the anaesthetic machine and breathes quietly through and around the Magill tube. He is able to hold his breath as directed whilst the radiograph is taken. The child lies quietly while the films are developed and further opaque medium can be injected to outline any segments shown to be inadequately filled. All that is needed is replacement of the polythene tube—a simple matter.

While the best bronchograms are obtained when the patient is conscious and cooperative, the method can still be applied to the sleeping child. Occasionally the child on waking indicates in no uncertain fashion that he does not intend to cooperate. In these circumstances it is desirable to keep him asleep with a further dose of thiopentone. The local anaesthetic prevents bronchial irritation and allows for a light sleep and natural respirations which help to ensure a good bronchogram.

When adequate bronchograms have been obtained the medium is aspirated through the No. 8 gum elastic catheter via the Magill tube. These are then both removed. This action usually provokes coughing and causes the child to bring up further amounts of 'dionosil'. The child is sent back to the ward with the examined lung uppermost. The whole procedure usually takes from 15 to 20 minutes. Nothing is allowed by mouth for two hours until the local anaesthetic has worn off. Postural drainage is continued in the ward until the bronchi are clear.

Discussion

It will be seen that part of the success of this method is dependent on adequate preparation of the patient along the lines indicated. This has meant that routine bronchoscopy and suction before bronchography has not been necessary and thus this stimulation to further secretion and spasm has been avoided. Secretion is usually satisfactorily removed by a catheter through the Magill tube, and only in two or three cases has it been necessary to carry out bronchoscopy before passing the Magill tube.

Oily 'dionosil', 60% w/v, was chosen because it gives radiographs of sufficient contrast; in addition, it does not flow out into the alveoli rapidly and also is absorbed quite quickly, usually in about 72 hours. We have experienced few side-effects from it and it is much less irritating than the aqueous preparation. Failure to shake the solution adequately did lead to bronchograms of poor contrast on one or two occasions. We had the impression that the contrast factor varied with the particular batch of the preparation.

The anaesthesia involves what may appear to be rather large quantities of 'xylocaine', namely, up to 8 ml. in small children and more in the bigger ones. In practice there have been no ill-effects. The amount used is about 0·13 g. per stone body weight and probably not all this is absorbed. On a weight basis this is equivalent to the amount used in complete safety in over 300 local anaesthetics for thoracoplasty in adults by one of us.

If the recovery of the patient from the anaesthetic for intubation is delayed then it is important to

decide whether to prolong it with additional thiopentone or to await complete return to consciousness. Attempts to carry out bronchography at this stage are invariably marred by the child's uncooperativeness as he returns to consciousness. One of the minor disadvantages of the method in our early cases lay in the difficulty of estimating accurately the minimal amount of thiopentone required. Delayed recovery from the intubation anaesthetic may lead to a considerable hold up in the *x*-ray department, a point of some practical importance. With increasing experience this disadvantage was largely eliminated.

The fact that the patient is no longer connected to the anaesthetic machine during the actual bronchography greatly facilitates the filling of the various lobes. His respiration is quiet and natural, and cooperation is good during posturing since he is not apprehensive. While the radiographs are taken the child will usually cooperate by holding his breath as directed. At the stage of unconsciousness at which we do the bronchogram we have been interested to note that little is retained in the child's memory, a point of considerable practical importance when the same procedure may have to be carried out on the opposite lung a week later. The child leaves the *x*-ray department conscious and this makes transport back to the ward and also nursing care much easier.

About a quarter of our cases required extra thiopentone to keep them asleep. The respirations are quiet and natural. The disadvantages are that the radiographer is without the child's cooperation and also that the final films are not of such good quality as those obtained in a conscious child.

In all our cases the airway has been good and in no instance has cyanosis occurred. With the small Magill tube the total cross section of rubber obstructing the airway at the narrowest point—the larynx—is small. The tube causes little trauma in its passage and in addition to its main function provides a good airway should aspiration prove necessary.

Although it is possible to obtain bilateral bronchograms simultaneously, some children will develop cyanosis and anoxia; this is partly due to obstruction of many terminal bronchioles with the medium, and partly to the increased secretions that occur during anaesthesia. The fact that we have avoided carrying out bilateral bronchography at the same time probably explains to some extent why we have not experienced cyanosis and anoxia with this technique.

We feel that this method is reliable and safe. It causes minimal trauma, both physical and mental, to the child. It has given us 95% of good bronchograms.

THROMBOCYTOPENIC PURPURA AND CHICKENPOX

BY

R. G. WELCH

From St. Thomas's Hospital, London

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Examination of the bone marrow in thrombocytopenic purpura shows two main patterns: the megakaryocytes are either deficient or else present in normal or even increased numbers. The former group results from depression of the marrow as by poisoning or mechanical displacement of the cells themselves by foreign tissue in leukaemia, infiltration with malignant cells, replacement with bone or fibrous tissue and other similar conditions. The group with a relatively normal appearance has been found to include cases due to the presence of anti-platelet bodies in the serum, to hypersplenism, to specific allergic responses to certain drugs such as 'sedormid' and 'quinidine' and others which seem to follow sufficiently closely on an infection for it to play some part in producing the condition. The following three patients developed purpura after chickenpox, although the third also had a large haemangioma, a condition itself incriminated in the past in the pathogenesis of thrombocytopenic purpura.

Case Reports

Case 1. D.W., a 6-year-old girl, 10 days after the onset of a mild attack of chickenpox developed bruises over the hips, arms and legs and in the next few nights bled a little from the gums. A week after the onset her platelet count was 106,000 per c.mm. and the Hess test strongly positive. The white cell count was normal. Four days later the platelet count had fallen to 30,000 per c.mm. and a week later to 20,000 per c.mm., though no fresh bruises had appeared in that period. The bone marrow was normal, the bleeding time 14½ minutes, and there was no splenomegaly. Sporadic bruising persisted for about 10 weeks, but three months after the onset of the chickenpox the platelet count was normal and the child well.

Case 2. P.R., a woman aged 26, noticed bruising on the limbs 14 days after the onset of chickenpox contracted from her nephew. Thirteen days after the onset her nose bled and two days later she started a very heavy period which persisted for more than 10 days. She had 70% haemoglobin and 3·3 million red cells per c.mm., when admitted a month after the onset of bruising, and 25,000 platelets per c.mm. The white cell count was normal. The Hess test was positive, and the bleeding time 12 minutes. The spleen was not palpable. After 10 days in which the platelet count fluctuated from 25,000 to 118,000 she was given 50 mg. A.C.T.H. six-hourly for six days, during which time the platelets rose steadily to 232,000, only to fall subsequently. She continued to bruise for some weeks and had a further heavy period eight weeks after the previous one, but was well four months after the onset of chickenpox. Of the three patients, this one alone had taken drugs before the onset of purpura—a few compound tablets of aspirin, phenacetin and codeine which she has taken before and since without ill effects.

Case 3. L.G.C., a girl aged 19 months, who has a large haemangioma covering the left pectoral area, four or five weeks before the onset of bruising developed a crop of spots thought to be due to chickenpox which was then epidemic. Three weeks after the purpura started she was admitted to hospital covered with bruises and purpuric spots. Bleeding had occurred into the haemangioma. Investigations showed 16,000 platelets per c.mm., 75% haemoglobin, 13,000 white cells (60% lymphocytes, 3% polymorphs, 2% monocytes, 2·5% eosinophils, 2·5% band polymorphs, and 1% each of myelocytes, metamyelocytes and myeloblasts). The bleeding time was prolonged, the Hess test markedly positive and the spleen was not palpable. The marrow showed slight normoblastic hyperplasia and abundant megakaryocytes, but no evidence of platelet formation. Bruising ceased and the platelets rose rapidly after admission so that five weeks after the onset of the purpura she was well.

Discussion

Clinically, thrombocytopenic purpura appears in two forms, the acute and the chronic: these three cases follow the acute pattern. Hirsch and Dameshek (1951) summarized the differences. The acute type shows no special sex incidence, has an acute onset, usually as purpura and bruising in a person, often a child, with no preceding history of any unusual bleeding and no marked family history of the condition or even of easy bruising. There may well be a lymphocytosis or eosinophilia in the peripheral blood smears and similar changes in the marrow. The megakaryocytes are normal or

increased in number, but show diminished production of platelets (Dameshek and Miller, 1946). The course is towards spontaneous and permanent recovery in a very short time—at the most four months, frequently a few weeks. The chronic type has a definite predilection for females: the patient often presents with bleeding (especially menorrhagia at puberty), but there is frequently a past history of easy bruising or excessive bleeding from minor injuries. Other members of the family may have been affected, and without treatment the condition remits and recurs over many years, although even in remission the platelet count is abnormally low.

There seems to be little doubt that many cases of thrombocytopenic purpura follow infections—particularly in childhood—and the thrombocytopenia tends to run the acute course leading usually to rapid recovery. McLean, Kreidel and Caffey (1932) reported infection in 12 of 21 children, occurring within 22 days of the onset of symptoms of purpura (two cases of measles at the 14th and 19th day of illness, one of pneumonia on the 22nd day and nine infections of the upper respiratory tract severe enough to cause fever, convulsions, cough, sore throat or nasal discharge; two had a maxillary sinusitis). Rosenthal's (1939) figures give infection in 12 (11 children) of 153 cases surveyed: five with glandular fever, two upper respiratory tract infections, and five after measles, chickenpox and scarlet fever. Heinild and Lindgren (1949) analysed the histories of 113 children and classified 63 as following infection (the infection as a rule within one or two weeks of onset). Twenty-one had had an upper respiratory tract infection, often streptococcal, nine had tuberculosis, seven sepsis, three Calmette vaccination, two followed wound infections, two rubella, two parotitis, one measles, one chickenpox and one diphtheria. The other 14 were labelled unknown infections. Hirsch and Dameshek (1951) had three cases following chickenpox, two after measles and rubella and two after the common cold in 18 examples of acute thrombocytopenic purpura, and noted that exacerbation in the chronic type followed infection in several. Clement and Diamond (1953) found infections in 65 of 96 children, the majority again in the upper respiratory tract, but seven had a more serious illness—rubella, chickenpox, infectious mononucleosis and pyelonephritis. Robson (1954) records that 32 of 56 cases of purpura in children were closely related to acute infection—commonly streptococcal—and 23 of these were thrombocytopenic; the other nine showed vascular fragility only. On the other hand Newton and Zuelzer (1951) were more sceptical of the part played by infection. Despite careful questioning they were unable to elicit a history of any infection in 22 of 47 cases seen and the rest had had for the most part only trivial infections—mild coryza or sore throat—although six had had measles within five weeks of the onset of symptoms. These seven papers in fact record 216 of about 500 cases of thrombocytopenic purpura in children as following infections. Excluding Robson's series where the infections are not defined, 50 of the cases (10%) followed a specific infective illness, for the most part the acute exanthematous illnesses of childhood.

Apart from these larger series, the occurrence of thrombocytopenic purpura after measles has been reported recently by Fisher and Kraszewski (1952), after rubella by Ackroyd (1949), after infectious mononucleosis by Ogilvie and Parry (1952), and by Volpe, Sparks and Mautner (1953), and each has reviewed the previous literature. Belber, Davis and Epstein (1954) have recorded this illness after cat scratch fever, whilst Box (1933) reported several instances after scarlet fever. Cohen (1936) reported thrombocytopenic purpura in a 6-year-old boy, starting six days after the rash of chickenpox, and quotes Tancredi who wrote of two cases of purpura without thrombocytopenia in children (aged 3 and $2\frac{1}{2}$) following chickenpox on the sixth and fifth days respectively. Cohen and Bansmer (1947) reported the case of an 11-year-old boy who bled into the vesicles on the third day of illness and subsequently elsewhere, and who had thrombocytopenia. They found references to 12 cases of haemorrhagic chickenpox, only four with significant haematological data, all of which recovered rapidly as did this child. Marsden and Coughlan (1952) wrote of a possible case of thrombocytopenic purpura in chickenpox starting on the third day of illness in an adult male and Hansen (1953) of a 13-year-old girl with a definite lack of platelets with symptoms starting after three days of illness. Stoesser and Lockwood (1938) watched a boy, nearly 4 years old, with chickenpox develop bruising on the fifth day of illness, then larger ecchymoses, and finally dry gangrene of both legs before recovering. He had thrombocytopenia, as did a somewhat similar but fatal case labelled purpura fulminans in an 11-year-old girl (McGovern and Dawson, 1954) who started bruising on the fourth day of illness, developed large ecchymoses on the thighs in the next two or three days and died within 30 hours of admission to hospital on the sixth day.

From all of this evidence four points emerge. First, that many infections, mild or severe, viral or bacterial, can, on occasion, be followed by thrombo-

cytopenic purpura. Secondly, this is not a common occurrence, but whilst it is impossible to estimate the frequency, the constant pattern in all these reports suggests that the relationship is more than coincidental. Thirdly, the time between the onset of the preceding illness and the start of the purpuric symptoms can vary from a day or two to four or five weeks. Most often there is an interval of about a week between the two—in the exanthematous illness at about the time the rash is beginning to fade. Finally, there is no relationship between the severity of the original illness and the subsequent development, or indeed the severity when it does develop, of purpura.

It is accepted that in thrombocytopenic purpura there is an increased capillary fragility as well as a diminished platelet count, and whilst changes in the one usually parallel those in the other, this is not always so. Clinically it is well recognized that in recovery the bruising and bleeding may diminish before there is any demonstrable rise in the platelet count. Experimentally Bedson (1922) showed that an extensive though temporary reduction in the platelets produced no purpura in the rabbit, but that injection of an antiplatelet serum into the guinea-pig first damaged the capillary endothelium and later, when the platelets had become greatly reduced in number, red cells leaked through the capillary wall into the surrounding tissues; there were not enough platelets to make good the deficiencies in the vessel wall. Macfarlane (1941) observed by microscopy that the capillaries in thrombocytopenic purpura were distorted and failed to contract properly when punctured. Subsequently Robson and Duthie (1950) have shown that capillary fragility is reduced by A.C.T.H. and cortisone, and it is thought that much of the beneficial effects of these drugs in this condition is due to this rather than to any change in the platelet count (Faloon, Greene and Lozner, 1952).

Tocantins (1938) states that in the acute stage of infectious diseases there is in general a thrombocytopenia which gives place at the termination of infection to a moderate increase. Perlman (1934) found a rather constant tendency for the platelet count to drop below normal in a series of 50 cases of measles in the incubation period, during the height of the eruption and during the fastigium, and said the same phenomenon also occurred in the other acute exanthemata though not as consistently as in measles. Ackroyd (1949) studied the platelet count and capillary fragility in five patients developing rubella, and found a fall in the platelet count in all (though never below 130,000 per c.mm.) for a variable period up to four weeks, and an increase in capillary fragility in four. These findings, together with some damage to the skin capillaries by the toxins causing the rash, would explain the occurrence of bleeding into the rash in the acute stage of certain infectious fevers, *e.g.*, haemorrhagic measles, but are unlikely to be the whole cause of true purpura occurring after an interval.

The presence of circulating platelet agglutinins has been shown in many cases of idiopathic thrombocytopenia (Harrington, Sprague, Minnich, Moore, Aulvin and Dubach, 1953; Stefanini, Plitman, Dameshek, Chatterjea and Mednicoff, 1953), but seldom in the acute type (Stefanini and Dameshek, 1953), nor does the plasma of the acute case produce any effect when transfused into a normal person. Volpe *et al.* (1953) have suggested hypersplenism as the possible cause of the purpura in their case following infectious mononucleosis. Though by no means negating this suggestion, it is remarkable how infrequently the spleen is palpable in the acute cases.

The acute onset of new symptoms after a brief quiescent period following an infective illness suggests an allergic cause: a hypersensitive response by the individual to the infecting element. The capillary changes in acute glomerulonephritis or in urticaria are evidence that such hypersensitivity can affect blood vessels. Clement and Diamond (1953) found a positive family history of allergic disorder in 30% of their 96 cases and a past personal history in 15·5%. Newton and Zuelzer found that only nine of 44 (21%) had had some allergic disorder previously and in 10 others there was a history of allergy in the preceding two generations. Whether the allergy affects only the capillary wall, or is responsible for inhibiting platelet production from the megakaryocytes as well, is not clear. Dameshek and Miller's (1946) description of the marrow suggests inhibition of the marrow function. Tidy (1926), however, suggested that the thrombocytopenia in purpura was secondary to the capillary damage, all the circulating platelets being used in a vain attempt to plug the leaking capillaries and the demand exceeding the supply. Lloyd (1944) thought this might be the cause of purpura in his case following mononucleosis.

Is there any common factor in all these examples of thrombocytopenic purpura following infection? It is, of course, possible that in each case there is the same organism present as secondary invader in the upper respiratory tract or skin lesions and it is in response to this that the purpura occurs. Little attention has been paid in the published series to the bacteriology, and further investigations on these lines in the future may prove illuminating. In the

light of our present knowledge it seems that the most likely mechanism is that of an allergic response to the infection.

The third patient described above presents an additional interesting feature, and one which may be relevant to her history of purpura. Her chickenpox probably occurred four or five weeks before the onset of thrombocytopenia—the date was difficult to define—and this is longer than most of the reported cases. She had, in addition, a large haemangioma on the chest, and the combination of acute thrombocytopenia and haemangioma has been noted on several occasions. Weissman and Tagnon (1953) found five reports on infants and added two cases of their own; they suggested this was enough to establish a new syndrome. All were infants or young children, and the thrombocytopenia appeared at the time when the angioma was fully developed. Other cases are recorded by Schoo (1952) in a newborn infant, White Franklin and Williamson (1953) two cases, Good, Carnazzo and Good (1955) three cases, and Meeks, Jay and Heaton (1955), a single case—14 examples in all. Good *et al.* noted the presence of platelet thromboses in the vessels of the haemangioma and suggested that sequestration of platelets in the tumour accounted for the thrombocytopenia. Incidentally, the fatal case described by Silver, Aggeler and Crane (1948) had exanthema subitum a few weeks before the purpuric symptoms started so the condition might be considered as post-infective. On the other hand, in the case reported here the coexistence of haemangioma with thrombocytopenia may, as in the others reported, be purely coincidental. Apart from evidence of bruising into it, the growth showed no change during the purpuric episode, and the course of the purpura was that of a typical acute thrombocytopenia. The patient had received no radiotherapy.

Summary

Three cases of thrombocytopenia purpura following closely on chickenpox are reported. This condition follows many different types of infection on rare occasions and it is thought that the most likely cause is an allergic response to the infecting organism. The condition is self-limiting and the prognosis usually excellent.

One of the patients reported had also a large haemangioma, and the combination of this growth with thrombocytopenic purpura has been reported previously.

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THE PATTERN OF THE ELECTROLYTE EXCRETION IN THE URINE OF BABIES BORN TO DIABETIC MOTHERS

BY

THOMAS STAPLETON

From the Paediatric Unit, St. Mary's Hospital Medical School, London

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The purpose of this investigation was to determine whether the electrolyte excretion in the urine of babies born to diabetic mothers is within the normal range. It seemed possible that the electrolyte excretion might be abnormal because these babies tend to have a greater birth weight and to show a greater percentage loss of weight in the first week of life than the general range of newborn infants.

Methods

The babies born to diabetic mothers in the Maternity Unit at St. Mary's Hospital during a period of two and a half years were studied. The urine passed during the first 72 hours after birth was collected. The babies were given no food during this time, although two (Babies L. and C.) were given a little water on the second and third days and two (Babies B. and A.) on the third day. The urine was analysed for sodium and potassium by flame photometry and for chloride by a modification of Volhard's method.

Satisfactory collections were made in five of the seven infants born to diabetic mothers during the period of the investigation; in one case (Baby T.) analyses for only 60 hours after birth are reported. (In one case some of the urine was lost. One infant weighed only 3 lb. at birth and collections were not attempted.)

Results

In the Table the approximate gestational age, the mode of delivery, the birth weight and the loss of weight as a percentage of the birth weight are shown.

In Figs. 1 to 3 the sodium, potassium and chloride outputs in the urine are shown superimposed on the range found in normal infants (calculated from the data of Hansen and Smith, 1953). The cases have been grouped according to the standards for gestational age adopted by the same authors: more premature (under 36 weeks' gestation), less premature (36 to 38 weeks' gestation), and full-term (39 to 40 weeks' gestation). Baby T. is classed in the 'more premature' group because of the obstetric opinion that the gestational age was probably less than 36 weeks, an impression confirmed by the greater percentage loss of weight during the first few days of life.

TABLE
BABIES BORN TO DIABETIC MOTHERS

Baby	Mode of Delivery	Gestational Age (weeks)	Birth Weight (kg.)	Weight Loss (%)
B	Caesarean	40	5·469	9·6
L	Normal	39	2·748	7·9
C	Normal	36	3·106	7·1
A	Caesarean	36	3·669	10·5
T	Caesarean	36	4·023	16·5

Discussion

Standards of Comparison. It is difficult when studying physiological functions in the newborn to know what standard of comparison to use. As the weight of a newborn baby changes from day to day, it would be unsatisfactory to compare the electrolyte excretion on the basis of the total body water as has been suggested by McCance and Widdowson (1952) for comparing renal functions at different ages. For the same reason the birth weight is unsatisfactory as a more oedematous or a more premature baby will lose more weight than a non-oedematous or a full-term baby. The lowest weight of the baby during the first week of life would seem to correspond from case to case most closely to the lean body mass, thus eliminating as far as possible variations due to differences in gestational age or in oedema. Some of the babies were born normally and some by Caesarean section. Furuhjelm (1954) has shown that, after the first three days, there is a slight difference between the weight loss of infants born by normal delivery or Caesarean section after the onset of labour pains on the one hand, and those born by Caesarean section without labour pains on the other. Therefore, the electrolyte excretion for the first three days after birth is expressed in milliequivalents per kilogram of the lowest weight reached by each baby during the first three days. Hansen and Smith (1953) studied the electrolyte

excretion in infants born at different gestational ages and their results have been recalculated so as to show a normal range.

Electrolyte Excretion. When compared on the above basis the urinary excretion of electrolytes is within normal limits for the particular gestational age. The small amounts of water given to four of the infants is unlikely to have influenced the electrolyte excretion, as Hansen and Smith (1953) showed that the electrolyte excretion in normal newborn babies was unaffected by water intake. Zetterström and Åberg (1955) in their study of infants of diabetic mothers obtained similar results during the initial fasting period, although they considered that the potassium excretion might be less than in other premature infants with oedema. This trend is seen in Baby T., but it is doubtful whether the difference is significant. No evidence has been obtained in this study to favour the suggestion that there is a disturbance of electrolyte metabolism, made by Björklund (1953), who studied the electrocardiogram of babies of diabetic mothers.

FIGS. 1-3.—The excretion of sodium, potassium and chloride during the first 72 hours of life in five babies born to diabetic mothers.

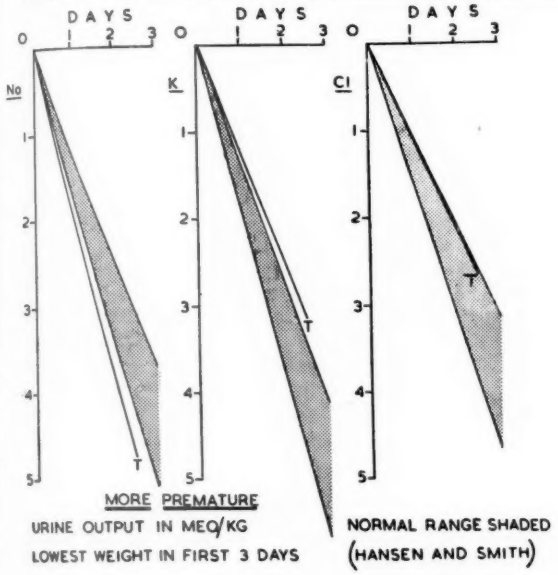

FIG. 1.

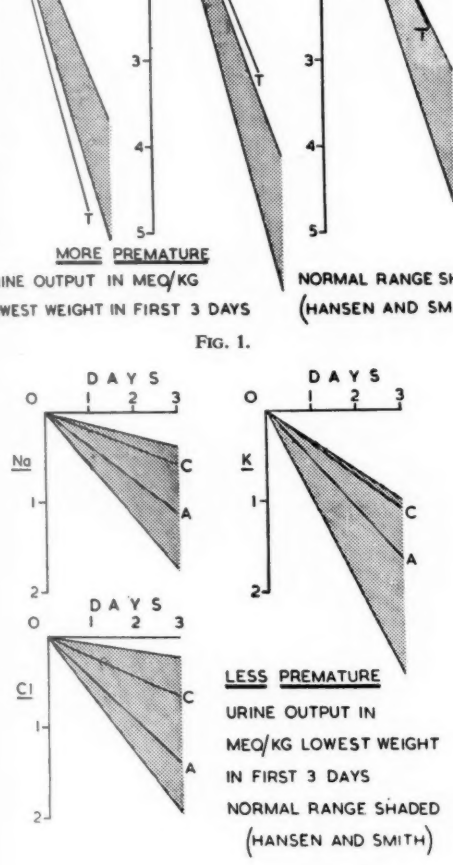

FIG. 2.

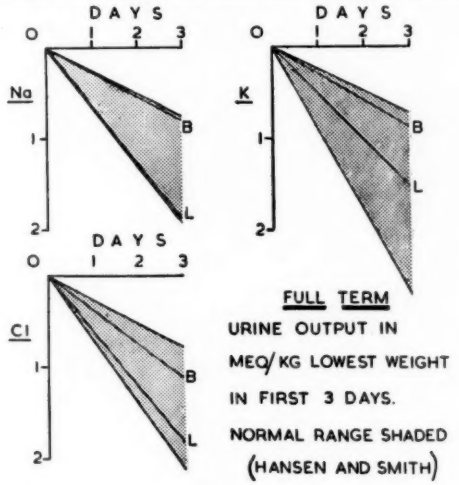

FIG. 3.

Summary

The electrolyte excretion in the urine during the first three days of life of five babies born to diabetic mothers was studied.

Taking the excretion in milliequivalents per kilogram lowest weight during the first three days after birth as the standard for comparison, no abnormality in the excretion of sodium, potassium or chloride was found.

The differences in electrolyte excretion between cases could all be accounted for by differences in the gestational age.

This investigation was suggested to me by Dr. W. M. Wallace, when working in the Children's Hospital, Boston.

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REMARKS ON THIRTY-THREE CASES OF SUBDURAL EFFUSION IN INFANCY

BY

E. HERZBERGER, Y. ROTEM and J. BRAHAM

From the Departments of Neurosurgery, Paediatrics and Neurology, Tel-Hashomer Government Hospital, Tel-Aviv, Israel

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Following the pioneer work of Ingraham and Matson (1954), the diagnostic possibility of subdural effusion in infancy has excited the interest of paediatricians and neurosurgeons. Guthkelch (1953) remarks that the condition may be regarded as one of the most frequent neurosurgical disorders in infancy, a striking observation when it is considered that up to 10 years ago the diagnosis was rarely made. The absence of a clear history of trauma in many cases, together with the discovery that effusions may follow meningitis, has led many paediatricians to perform subdural taps in a wide range of clinical conditions. Although otherwise unsuspected effusions may be revealed in this way one may be left with an uneasy feeling that the condition is being over-diagnosed, the more so as recognition of the condition carries with it in many cases a firm recommendation to craniotomy.

The purpose of this paper is to present our personal experience of 33 cases treated in the Tel-Hashomer Hospital between 1953 and 1955, and our views regarding various aspects of the problem.

The babies were of an age varying from 1 day to 24 months and in the main were from new immigrant families living in poor conditions. Eighteen were admitted from other institutions with an established diagnosis of subdural effusion.

Aetiology

In 15 cases there was an antecedent purulent meningitis; the causative organisms were *Haemophilus influenzae*, pneumococci or meningococci. In three cases a reasonably certain history of birth injury was obtained, and in one a history of a fall. One case was of *Torula histolytica* encephalitis.

In 13 cases no certain history of trauma could be obtained. It must be emphasized that cooperation with the parents was in many instances not satisfactory and in the kind of homes from which the children came there was ample opportunity for unrecognized trauma.

The pathogenesis of the effusion has already been adequately discussed (Guthkelch, 1953). It should be added that the role of the tap itself is not entirely unsuspect, and it is not always possible to deny that needling may indeed be the cause of local effusion, particularly where it is repeated when initially unproductive. That this is at any rate not always the case was demonstrated in 32 cases of the present series where the first tap did, in fact, reveal fluid. Biochemical examinations of the fluid confirmed the naked-eye impression that it was not identical with cerebrospinal fluid; protein values of the order of 180 to 3,400 mg. % were consistently obtained, whereas in the C.S.F. the average lay between 20 and 180 mg. %.

Pathology

Opportunities for observation of meningeal and cerebral changes were provided by burr holes (22 cases) and post-mortem examination (seven cases). In three of the latter, burr holes had been made previously, and it was possible to confirm the conclusion that they permitted a reliable impression to be obtained of the state of the underlying structures.

In this way clear evidence of brain damage (excluding simple reversible compression) was seen in 16 out of 22 operated cases. The changes included (*a*) atrophy, microgyria, scarring—varying in degree from moderate to most severe; (*b*) oedema, greyish-red discoloration, purulent cortical softening, milky opacity of the pia and pial congestion—these latter occurring chiefly in post-meningitic patients.

Of the seven cases examined at necropsy, one (Case 3) was a baby dying on the day of birth with a large right-sided subdural haematoma (undiagnosed). One died following purulent meningitis and was found to have a thalamic abscess. In four infants the effusion developed during the course of an illness characterized otherwise by gastro-enteritis, malnutrition, bronchopneumonia and a

poor or moribund state on admission. The earliest of these (Case 2), undiagnosed before death, showed cerebral oedema as well as the effusion, and in the others the examination disclosed a very small shrunken firm brain, thrombosis of the superior longitudinal and other dural sinus and cortical venous thrombosis. Subdural membranes were present and a fluid-containing space of 2·5 cm. in average width separated the dura from the brain. Similar changes were seen in Case 25, with the difference that section of the brain here showed many cystic cavities containing white gelatinous material. Histological examination of this white material disclosed *Torula histolytica*. Figs. 1 and 2 show the high degree of atrophy of the brain seen in Case 22.

A surprising find in this series, and one which we consider of importance in relation to the general management of these patients, was the inconstant relationship of the degree of brain damage on the one hand to the presence and extent of membrane on the other. Variations in this association could be fitted into four groups as follows:—

Group I: No membranes, no macroscopic brain damage.

Group II: Thin, ill-defined membranes, no macroscopic brain damage.

Group III: No membranes, but macroscopic brain damage.

Group IV. Well-defined membranes with macroscopic brain damage.

The prognostic and therapeutic implications of these observations are discussed below.

Clinical Features

The majority of the patients fell into two well-defined clinical groups.

The Post-meningitic Group. This comprised 15 cases. The usual indication for the subdural tap was failure of adequate clinical improvement in spite of appropriate antibiotic therapy, with or without additional neurological complications.

Case 12. An 11-month-old child with *Haemophilus influenzae* meningitis remained febrile after one week's treatment. Right-sided convulsions appeared, followed by a complete right hemiplegia. A subdural tap disclosed a unilateral, left-sided collection of xanthochromatic fluid containing 1,300 mg. % protein and 160 leucocytes. Persistence of the fluid after four taps for

FIG. 1.—Extreme atrophy of the brain in Case 22.

FIG. 2.—Thrombosed cortico-dural vessels are seen crossing the greatly enlarged subdural space (Case 22).

two weeks led to the performance of a left temporal burr hole which revealed a thick, friable, greenish-brown membrane applied to the pia arachnoid. At the subsequent craniotomy the membrane was stripped off fairly easily except for one small part where it was firmly adherent to the cortex. The child made a gradual, but full recovery.

The Non-meningitic Group. The non-meningitic group can be divided into 'cerebral' and systemic types.

A 'CEREBRAL' TYPE. The four infants in this group presented with convulsions, vomiting, some evidence of mental retardation and bulging fontanelle, in various combinations. In three there was a certain or probable history of birth injury; one was diagnosed later as torulosis.

'SYSTEMIC' GROUP. In these 12 infants the clinical features were such as are appropriate to a diagnosis of malnutrition, gastro-enteritis or bronchopneumonia, either alone or in combination. Their general condition was very poor and they failed to respond to a régime of hydration, adequate feeding and the treatment of infection. The first case in this group came to necropsy with the effusion undiagnosed, thus providing a stimulus to the performance of exploratory subdural taps in the infants with a similar clinical background and unsatisfactory course.

As the number of cases in this group indicates, the exploration was rewarding to a surprising degree, and this constitutes a unique and special feature of the series presented here. One can hardly disprove that trauma had played no part in the aetiology; on the other hand where trauma was reasonably certain the clinical picture was quite different. Again, the discovery on so many occasions of a collection of fluid at the initial subdural tap might seem largely to allay any natural suspicions that the needling caused the effusion. The reversal of the general condition in most instances after treatment of the effusion is further evidence of probably more than circumstantial significance.

Case 2. An infant, aged 5 months, was admitted with one week's history of diarrhoea and vomiting before admission, and during the last few days swelling of the legs. On admission there was fever, non-pitting oedema, rickets, malnutrition and enlargement of spleen and liver. The blood protein level was 2·5 mg. % with 1 : 1 albumin-globulin ratio; Hb 10·6 g. %, leucocytes 6,200 per c.mm. The administration of fluids (11 infusions), vitamins and antibiotics did not succeed in bringing about any improvement. Bronchopneumonia appeared and the general condition deteriorated and the baby died six weeks after admission.

At necropsy, in addition to the expected changes in the lungs, large bilateral subdural effusions and moderate cerebral oedema were found. There was no membrane formation.

Case 33. A 3-month-old infant was admitted to another hospital because of gastro-enteritis of one week's duration. There was severe malnutrition and dehydration with anaemia (Hb 8·4 g. %, leucocytes 4,200 per c.mm., red blood cells 2·7 millions per c.mm.). Antibiotics and the administration of fluids produced no response. Subdural taps showed bilateral accumulations of fluid containing 255 mg. % protein and 3 cells per c.mm. Lumbar puncture on the same day yielded C.S.F. containing 50 mg. % protein and 27 cells per c.mm., and 5-10 ml. of fluid were removed from each side. The tap was repeated once, and the infant then referred to this hospital. Clinical improvement was already noted at this stage. One further tap was performed which was dry on the left; from the right side 3 ml. of fluid were aspirated.

One week later bitemporal burr holes were made and nothing abnormal found. The child continued to make a rapid recovery.

Two other cases, not fitting into the above major groups, are of some interest. One was a 4-month-old infant (Case 27) admitted because of hydrocephalus. This was of the communicating type, and during the course of investigations a thick membrane was discovered over the left hemisphere. Craniotomy and removal of the membrane did not influence the hydrocephalus in any way. The other (Case 5), an infant aged 9 months, suffered from intermittent and unexplained fever for several weeks. Because of the history of a fall some days preceding the onset of fever and some degree of bulging of the fontanelle, bilateral taps were performed and effusions found over both hemispheres.

Treatment

In seven of the cases (five post-meningitic and two 'gastro-enteritic') the effusions responded to evacuation by repeated taps, some 8-15 ml. of fluid being removed on each occasion. As it happened, the fourth tap in each of these patients was dry and no further action was taken in view of the rapid clinical recovery.

Failure of the effusion to respond to this simple measure led to the performance of burr holes in 22 patients. Fluid was evacuated and the brain and its coverings inspected. Membrane was seen in half of the infants submitted to this procedure. In two cases the membrane (unilateral) was thick, greenish and adherent to the arachnoid and was removed at subsequent craniotomy (the post-*Haemophilus* meningitis and the hydrocephalus cases respectively). In the remaining nine cases the membrane was thin, whitish and applied only to the inner surface of the dura, but not adherent to the arachnoid. Craniotomy, although contemplated,

was not carried out in the first place because of the very poor general condition of these infants. However, when it was seen that this minor procedure was followed by a considerable change for the better, the more formidable intervention of craniotomy was deliberately withheld in subsequent cases where this kind of poorly-developed membrane was found. In others visible brain damage seemed to preclude the necessity for craniotomy for removal of membrane which, not being applied to the brain, could presumably not be causing such damage.

Results

Repeated taps, from two to four in number, sufficed to bring about apparent cure in five meningitis cases and in two enteritis-malnutrition cases. All six of the 22 submitted to burr holes, in whom no brain damage was seen (Group I and II above), did very well. Of the Group III cases (brain damage without membrane), seven improved but were not considered to do as well as those without brain damage. One case in this group with universal spasticity of the limbs failed to respond in any way. Group IV (well-marked membrane, brain damage) with eight cases contained the most seriously ill children. Three died, three recovered to a degree comparable to that of the previous group and two were treated by craniotomy, with results as described. As seen from Table 1, the results correlate well with the degree of brain damage, the presence or absence of membrane being of less importance.

Discussion and Conclusions

From the clinical point of view our material seems to be of special interest because of the inclusion of a high proportion of cases—about one-third of the total—in which the clinical course would not normally be considered to be related to the presence of subdural effusion. The post-mortem findings in a missed case result in increased awareness of this possibility in infants with non-cerebral syndromes and an unsatisfactory clinical course. Other workers in this area are alert in seeking and detecting these cases (Levine, 1953) as is also shown above by the number of instances in which the infants were referred from other institutions with the diagnosis already established. It may be that the effusion in these cases can be related to the readiness of infants in a subtropical climate to develop dehydration, with consequent reduction in brain volume and thus the creation of an actual instead of a potential subdural space. Altered capillary permeability and local congestion due to marantic phlebo-thrombosis perhaps then constitute further pre-conditions for seepage into such a space. In 16 of these patients, brain damage was in fact seen, varying in severity from moderate oedema to pathogenetic bilateral atrophy with multiple sinus thrombosis. Another possibility, gastro-enteritis, may be regarded as yet another infection, liable to complication by intracranial venous thrombosis (Symonds, 1952). One may speculate that treatment by antibiotics and attention to fluid and electrolytic imbalance preserve life long enough to allow the further development of these effusions; this chain of circumstances could perhaps also account for their increased incidence in recent years.

From the neurosurgical viewpoint our approach has been conservative, and only two craniotomies were performed in the whole series. The decision not to perform this operation routinely on the discovery of membrane represents a departure from Ingraham and Matson's recommendations. We were satisfied at the time these children were treated that clinical recovery was either rapid and complete, or compatible with what could be expected in the light of existing brain damage. Final justification clearly must depend on a prolonged follow-up, with estimates of physical and intellectual development during the school years, the presence or absence of fits and perhaps repeated electroencephalographic studies.

TABLE 1

CLINICAL RESULTS IN RELATION TO PATHOLOGICAL FINDINGS

	Group I:* No Membrane and No Brain Damage	Group II: Membrane, but No Brain Damage	Group III: No Membrane, but Brain Damage	Group IV: Membrane, but Brain Damage
Excellent	9	3	—	—
Good	—	1	5	2
Moderate	—	—	3	1
Poor	—	—	1	1
Death	—	—	2	5

Excellent = full recovery within two weeks. Good = slow but continuous improvement until discharge and subsequently. Moderate = general clinical improvement but with delay in development according to age. Poor = mental and neurological defects with no improvement.

* Group I includes cases treated by taps without exploration of the subdural space.

SUMMARIES

Case No.	Age and Sex	Duration of Illness on Admission	Predominant Clinical Syndrome	Aetiology	C.S.F. Findings	Subdural Fluid F...	Tr... Taps On...
1	2½ months M	4 days	Purulent meningitis	Negative culture	1,900 cells, 157 mg. % protein	164 cells, 720 ... protein	...aps
2	5 months M	10 days	Gastro-enteritis, malnutrition, fever, bronchopneumonia	Negative culture	4 cells, 35 mg. % protein	Not diagnosed	—
3	1 day M	1 day	Convulsions, coma, bulging fontanelle	Birth injury	Blood-stained	Not diagnosed	—
4	9 months F	6 weeks	Gastro-enteritis, malnutrition	Negative culture	3 cells, 40 mg. % protein	20 cells, 350 ... protein	—
5	9 months F	7 weeks	Febrile state only, bulging fontanelle	Trauma of head at 7 months	2 cells, 25 mg. % protein	No cells, 400 ... protein	—
6	15 days M	1 week	Convulsions, bulging fontanelle	Birth injury	870 erythrocytes, 180 mg. % protein	No cells, 1,000 ... protein	—
7	12 months M	4-5 months	Mental deficiency, spasticity, bulging fontanelle	Birth injury	40 cells, 25 mg. % protein	No cells, 200 ... protein	—
8	4 months F	8 weeks	Purulent state after meningitis	*Haemophilus influenzae*	20 cells, 40 mg. % protein	No cells, 180 ... protein	—
9	5½ months F	3 months	Gastro-enteritis, malnutrition	Negative culture	4 cells, 35 mg. % protein	10 cells, 416 ... protein	—
10	3 months M	3½ weeks	Purulent meningitis	Pneumococci	860 cells (polynuclears), 187 mg. % protein	120 cells (polyn... tap 650 mg. % prote...	
11	5 months M	3 months	Gastro-enteritis, malnutrition	Negative culture	5 cells, 15 mg. % protein	260 cells, 675 ... protein	—
12	9½ months M	1 day	Purulent meningitis, later right hemiplegia	*Haemophilus influenzae*	2,500 cells (polynuclear) 180 mg. % protein	160 cells, 1,350 ... protein	—
13	2½ months M	2 days	Purulent meningitis	Pneumococci	1,400 cells (polynuclear), 165 mg. % protein	60 cells, 1,500 ... protein	—
14	4 months F	3 days	Purulent meningitis	Meningococci	4,000 cells (polynuclear), 182 mg. % protein	132 cells, 720 ... protein	3
15	6 months F	2 weeks	State after purulent meningitis	Meningococci	45 cells, 30 mg. % protein	900 cells, 1,500 ... protein	—
16	12 months F	1 day	Purulent meningitis	Pneumococci	5,000 cells (polynuclear), 205 mg. % protein	250 cells, 890 ... protein	3
17	9 months F	3 weeks	State after purulent meningitis	Negative culture	5 cells, 15 mg. % protein	120 cells, 450 ... protein	—
18	4 months M	4 weeks	State after purulent meningitis	Meningococci	66 cells, 25 mg. % protein	20 cells, 200 ... protein	—
19	5 months M	1 day	Purulent meningitis	Pneumococci	1,100 cells (polynuclear), 120 mg. % protein	269 cells, 1,350 ... protein	...t effusi...
20	13 months M	1 day	Purulent meningitis	Pneumococci	2,300 cells, 200 mg. % protein	68 cells, 750 ... protein	2
21	8 months ??	4 weeks	Gastro-enteritis, malnutrition	Negative culture	5 cells, 20 mg. % protein	No cells, 278 ... protein	—
22	7 months M	3 months	Gastro-enteritis, malnutrition, convulsions, spasticity, mental deterioration	Negative culture	8 cells, 25 mg. % protein	613 cells, 3,400 ... protein	—
23	?? ??	4 weeks	Gastro-enteritis, malnutrition, convulsions, fever	Negative culture	4 cells, 20 mg. % protein	5 cells, 180 mg. ... protein	—
24	5 months F	5 weeks	Gastro-enteritis, malnutrition	Negative culture	3 cells, 20 mg. % protein	No cells, 180 ... protein	—
25	6 months M	6 weeks	Convulsions, vomiting, bulging fontanelle	*Torula histolytica*	2 cells, 15 mg. % protein	25 cells, 425 ... protein	—
26	6 months F	4 months	Gastro-enteritis, malnutrition	Negative culture	5 cells, 28 mg. % protein	12 cells, 240 ... protein	3-4
27	7 months M	4 months	Large communicating hydrocephalus	Unknown birth injury? Degenerative?	No cells, 15 mg. % protein	No cells, 1,200 ... protein	—
28	10 months M	6 weeks	Gastro-enteritis, malnutrition, bronchopneumonia	Negative culture	No cells, 20 mg. % protein	52 cells, 1,800 ... protein	—
29	5 months F	2 weeks	State after purulent meningitis	Meningococci	33 cells, 40 mg. % protein	56 cells, 480 ... protein	3
30	4 months F	1 day	Purulent meningitis	Pneumococci	8,600 cells (polynuclear), 210 mg. % protein	8,250 cells, 780 ... protein	—
31	5 months F	8 days	Gastro-enteritis, malnutrition, bronchopneumonia	Negative culture	No cells, 60 mg. % protein	7 cells, 300 ... protein	— tap dry
32	3 months F	3 months	State after purulent meningitis	Negative culture	80 cells, 180 mg. % protein	200 cells, 720 ... protein	— ...l effusi... ...dural ...ps)
33	3 months F	4 weeks	Gastro-enteritis, malnutrition	*Bact. coli* O 111	27 cells, 50 mg. % protein	3 cells, 255 ... protein	by 3-4 ...al effusi...

* Left craniotomy.

SUMMARIES

ural Fluid F	Treatment		Operative or Post-mortem Inspection of Brain		Clinical Results
	Taps Only	Burr Holes	Membrane	Brain Damage	
cells, 720 m in	aps	—	—	—	Excellent
diagnosed	—	—	No membrane, bilateral large effusions	Generalized slight oedema	Death
diagnosed	—	—	Left subdural haematoma	Generalized oedema	Death
ells, 350 m in	—	Bi-temporal	Thin membrane, bilateral effusions	Bilateral atrophy of brain	Moderate
cells, 400 m in	—	Bi-temporal	None, bilateral effusions	None	Excellent
ells, 1,000 m in	—	Bi-temporal	None, bilateral effusions	Slight bilateral atrophy	Good
cells, 200 m in	—	Bi-temporal	None, bilateral effusions	Bilateral atrophy, microgyria, right	Poor
cells, 180 m in	—	Bi-temporal	None, bilateral effusions	Oedema and discoloration L.>R.	Good
ells, 416 m in	—	Bi-temporal	None, right effusion	Atrophy of brain, right, particularly frontal	Moderate
cells (polym ng. % prote	tap	—	Bilateral, thick	Oedema, generalized, abscess brain (rt. thalamic)	Death
cells, 675 m in	—	Bi-temporal	Bilateral, thin; bilateral effusions	Bilateral atrophy, slight	Good
ells, 1,350 m in	—	Left temporal*	Thick membrane, left effusion only	Oedema and discoloration, left	Good
lls, 1,500 m in	—	Bi-temporal	None, bilateral effusions	None	Excellent
cells, 720 m in	3	—	—	—	Excellent
ells, 1,500 m in	—	Bi-temporal	Slight bilateral	None	Excellent
cells, 890 m in	3	—	—	—	Excellent
cells, 450 m in	—	Bi-temporal	None, bilateral effusion	Slight bilateral atrophy	Good
lls, 200 m in	—	Bi-temporal	None, right effusion only	Bilateral oedema of brain R.>L.	Good
ells, 1,350 m in	—	Right temporal	None	None, slightly milky pia arachnoid	Good
lls, 750 m n	ht effusion 2	—	—	—	Excellent
ells, 278 m n	—	—	Thick, bilateral. Bilateral	Very marked bilateral atrophy of brain. Thrombosis of superior long sinus, right lateral sinus	Died. Condition so poor that operation was not contemplated
lls, 3,400 m n	—	Bi-temporal	Slight bilateral membranes, bilateral effusions	Very marked bilateral atrophy, sclerosis and scarring of brain	Died
s, 180 mg. n	—	Bitemporal	Thin bilateral membranes, bilateral effusions	Generalized atrophy of brain Multiple thromboses	Died
ells, 180 m n	—	Bi-temporal	Thin right membrane only, right effusion	Moderate atrophy of right brain	Moderate
lls, 425 m n	—	Bi-temporal	Slight bilateral membrane, bilateral effusions	Very severe bilateral atrophy of brain, intracerebral cysts containing white gelatinous matter. Multiple thromboses	Died. The diagnosis of torulosis was made post-mortem
lls, 240 m n	3-4	—	—	—	Excellent
lls, 1,200 m n	—	Left temporal *	Thick membrane, left only; left effusion	Very large hydrocephalus	Poor
ls, 1,800 m n	—	Bi-temporal	Slight membrane right only; bilateral effusions	None	Excellent
lls, 480 m n	3	—	—	—	Excellent
cells, 780 m n	—	Bi-temporal	Slight membrane bilateral; bilateral effusion	None	Excellent
s, 300 m n	— (tap dry)	Bi-temporal	Slight bilateral membrane; bilateral effusions	None	Good
ells, 720 m n	— l effusions dural ns)	Temporal burr hole, right only	No membrane	Right oedema of brain	Moderate
s, 255 m n	by 3-4 taps l effusion)	Bi-temporal for contra-lateral	No membrane, no effusions	None	Excellent

Summary

A series of 33 cases of subdural effusion in infancy is presented. In four only was there a reasonable certainty of a traumatic aetiology; 15 followed purulent meningitis and in 12 the effusion appeared in the course of a general illness with gastro-enteritis, malnutrition and bronchopneumonia.

Neurosurgical intervention was limited to burr holes in 22 cases; craniotomy for removal of the membrane was performed on two occasions only.

The immediate results of such conservative management were considered to justify withholding major surgery, though final opinion must wait upon a long follow-up.

It is a pleasure to acknowledge the cooperation of the paediatricians of the 'A' and 'B' Paediatric Departments of the Tel-Hashomer Hospital.

We are also much indebted to the physicians in charge of the Paediatric Departments of the Assaf Harofe (Sarafand), Zahalon (Jaffa), Rambam (Haifa), Schweitzer (Tiberias) and Hadassah (Tel-Aviv) Hospitals who referred many of the cases.

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BILATERAL WILMS' NEPHROBLASTOMA

BY

GERALD B. DOYLE

From the Department of Pathology, Coventry and Warwickshire Hospital, Coventry

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Comparatively few cases of bilateral Wilms' tumour have been described in the past 55 years. In 1897, Walker reviewed the literature over the previous 100 years and found 141 cases of Wilms' tumour of which 10 were said to be bilateral, but he gave no details of these. Hedrén (1907) described a remarkable case with apparent multicentric origin in both kidneys. In 1931, Kretschmer and Hibbs found two cases in a review of 17. Other isolated reports followed. Ueda (1935) recorded a single case; Ladd (1938) found one case in 45 reviewed; Herzog (1939) quoted some reports from the European literature of which two occurred in this century (Jemma, 1922; Nevinny, 1926). Campbell (1948) reported two cases diagnosed at necropsy; Barr and Schulte (1950) and Rusche (1951) recorded one case each. In a review of 74 cases diagnosed at The Hospital for Sick Children, Great Ormond Street, London, from 1925 to 1951, only one bilateral case occurred (British Empire Cancer Campaign Report, 1951), while a survey of the material in the Boston Children's Hospital, 1914-47, disclosed four cases in a total of 96 (Gross, 1953). Sheach (1953) added another report. The following description concerns a further case in a girl.

Case History

The patient was a girl of 3 years who had a fall while playing in the road. Radiographs at the time of this mishap showed no fracture of the dorsal or lumbar spines and no abnormality of the chest. In the following two months she had occasional bouts of vomiting and her mother noticed a gradual enlargement of the abdomen. Eventually the child was brought to her doctor who arranged admission to the City Hospital, Nottingham.

Examination revealed a pale, irritable child with a distended abdomen. There were some prominent veins on the abdominal wall, and a soft, painless mass could be palpated on the right side. There was no visible peristalsis. The child was apyrexial, and there were no enlarged tonsils or palpable lymph nodes, nor was there any evidence of cardiac or respiratory abnormality. Urinary examination showed a few red blood cells in the uncentrifuged specimen, but nothing else of note. A blood count gave haemoglobin 8·4 g., R.B.C. 4,050,000 per c.mm., W.B.C. 8,500 per c.mm. (polymorphs 52%, lymphocytes 45%, monocytes 3%).

A straight radiograph of the abdomen showed a large opacity due to a mass of soft tissue. Further investigations were precluded by the general poor condition of the child. Shortly afterwards she became extremely shocked and collapsed. A paracentesis abdominis was performed and about half a pint of straw-coloured fluid was aspirated. The patient's condition slowly deteriorated and she died the same day.

Necropsy. The body was that of a well developed but rather emaciated female child. There was some mucopus in the bronchioles. The heart was of normal pattern. The abdomen contained a large tumour mass in the region of each kidney (Fig. 1). The mass on the right side was the larger and on section appeared cystic; the cystic spaces, containing gelatinous material, were separated by wide bands of tumour tissue. The kidney was recognizable in the tumour mass. On the left side, beneath the capsule of the growth, there was recent haemorrhage which appeared to have originated within the tumour. The left kidney was also involved in the growth. There were a few enlarged lymph nodes near the mid-line but these showed no malignancy. The liver and spleen showed marked toxic changes. The other abdominal organs showed nothing of note.

Sections of both tumours showed the typical pattern of Wilms' nephroblastoma (Fig. 2). Sheets of undifferentiated tissue of embryonic type surrounded clumps of epithelial cells in which there were tubules of varying development.

Discussion

The rarity of bilateral Wilms' tumour suggests that such cases as do occur are usually multifocal in origin, and that direct extension from one kidney to another is unusual. Direct spread has occurred on occasion as in Kretschmer and Hibbs's second case (1931), but in most of the reported cases, including the present one, separate tumours appear to have originated in both kidneys.

The majority of cases terminate fatally, and death in this instance was almost certainly due to the severe haemorrhage occasioned by the rapidly growing tumour on the left side.

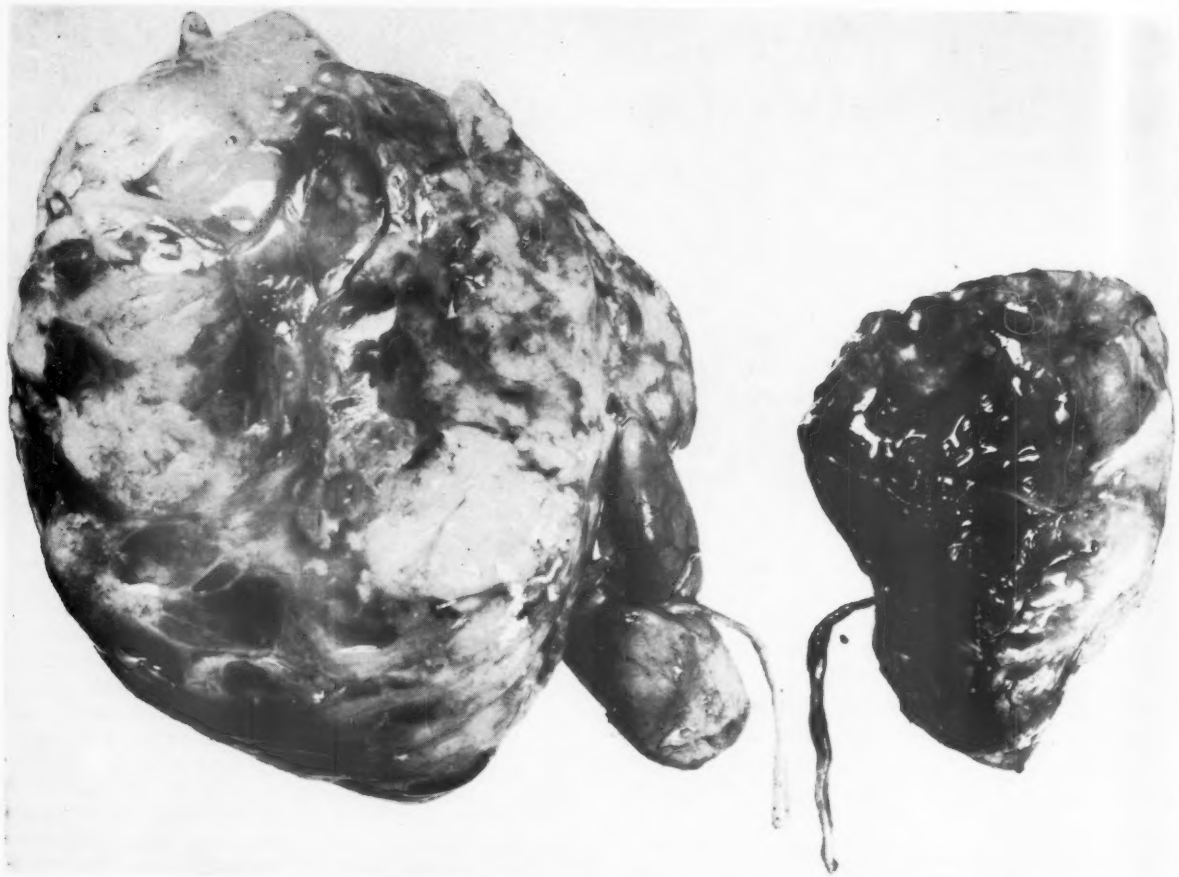

FIG. 1.—Cut section of tumours showing the right kidney and the haemorrhage on the left side.

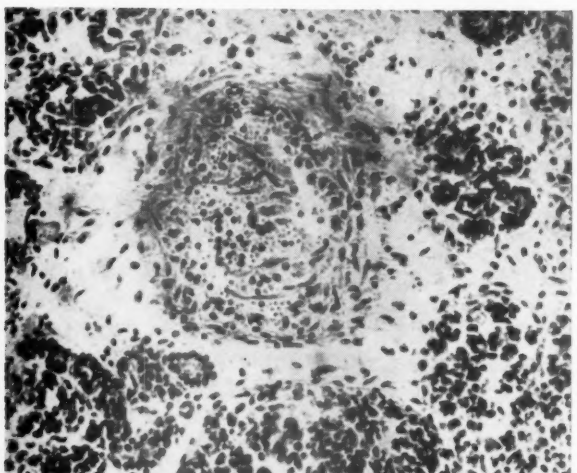

FIG. 2.—Typical Wilms' nephroblastoma with many small tubular structures. Haematoxylin and eosin ×100.

Summary

A case of bilateral Wilms' nephroblastoma is recorded with a brief enumeration of the other cases in the literature of this century.

I am indebted to Dr. A. P. M. Page under whose care the patient was admitted to hospital.

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HARLEQUIN FOETUS

BY

I. KESSEL and F. C. FRIEDLANDER

From the Transvaal Memorial Hospital for Children and the Department of Pediatrics of the University of the Witwatersrand

(RECEIVED FOR PUBLICATION SEPTEMBER 22, 1955)

Harlequin foetus, the most severe form of congenital ichthyosis, is a rare condition and infants suffering from the abnormality are pitiable objects. The first description of the condition is probably that of the Rev. Oliver Hart of Charleston, U.S.A., who, in 1750, recorded in his diary the description of a newborn infant with this severe type of skin disease. His description, which bears repetition, fits our case perfectly and is an excellent piece of clinical reporting.

> 'The skin was dry and hard and seemed to be cracked in many places, somewhat resembling the scales of a fish. The mouth was large and round and wide open. It has no external nose but two holes where the nose should have been. The eyes appeared to be lumps of coagulated blood, turned out, about the bigness of a plum, ghastly to behold. It had no external ears but holes where the ears should be. The hands and feet appeared to be swoln, were crumpt up and felt hard. The back part of the head was much open. It made a strange kind of noise, very low, which I cannot describe. It lived about eight and forty hours and was alive when I saw it.'

Most descriptions of the condition are similar to this one, quoted by Lattuada and Parker (1951) and written over 200 years ago.

Case Report

A white male infant, aged 4 hours, was admitted to the Transvaal Memorial Hospital for Children on October 5, 1954.

No history was obtained on admission, as the infant was sent in by ambulance unaccompanied. Subsequent questioning of the parents revealed that a previous infant had died at birth with a similar condition. There were several siblings who were all quite well and the parents were both fit and healthy. The pregnancy was uneventful.

The infant presented a striking abnormality of the skin, which was hard, horny and of a yellowish-white colour where the horny layer was thickest. In the body folds the skin was fissured and these cracks were an eighth to a quarter of an inch deep in some places. The underlying skin appeared red and not grossly abnormal in the cracks; there was some blood-stained ooze in these areas. The skin of the abdomen was severely affected, while the skin of the back and thorax was less thickened.

The skin of the face had the same appearance as that on the rest of the body. Ectropion of the upper and lower lids was so severe that there was complete eversion of both lids. The mouth was shaped like an O due to the severe hyperkeratosis. The ears were deformed.

The infant lay with the arms flexed at the shoulders and elbows and the hands flexed on the forearms. The thighs were flexed on the trunk and the knees and ankles were also flexed. This extreme flexion was due to the very thickened, inelastic skin. Bands of hyperkeratotic epidermis were present on several fingers and toes, causing deformities.

FIG. 1.—The general appearance of the infant.

Further examination revealed no other abnormality in any of the systems. The temperature was subnormal (96° F.).

The patient's progress was marked by extension of the fissuring and some loss of large flakes of hyperkeratotic skin, leaving a somewhat reddish, granular skin underneath. This more normal-looking skin persisted until death.

The infant was given a diluted sweetened condensed milk feed and managed to take this from a bottle. He passed meconium on the day after admission, *i.e.*, at about 20 hours of life, and thereafter passed one to three stools per day. The temperature remained subnormal for 72 hours and fluctuated thereafter between 98° F. and 98·6° F. Urine was passed, but it was not possible to estimate the amount.

As a previous case seen in this hospital had shown lower nephron nephrosis (acute tubular necrosis) at necropsy (Kessel and Javett, 1955) a blood urea estimation was done on the second day, revealing a level of 93 mg. %. On the fourth day the level of the blood urea had risen to 129 mg. %. The Ide blood test for syphilis was negative.

The further course was downhill and the infant died on the fifth day.

A skin biopsy taken from an area of extreme hyperkeratosis on the abdomen before death was reported on by Dr. H. Lurie, of the South African Institute for Medical Research, as follows: Section of this specimen of skin from the left flank showed solid hyperkeratosis. The granular layer was present and the rete Malpighii was acanthotic. The pegs tended to be flattened. There were a few small foci of intracellular oedema. In the dermis there were numerous follicles and sweat glands. The amount of elastic tissue was definitely diminished.

Necropsy was performed by one of us (F.F.) and apart from the gross external appearance noted above there was nothing remarkable noted macroscopically. The thyroid gland appeared normal in size, but unfortunately was not sent for histological study. Two sections of skin were sent, one from an area in the neck where the thickened epidermis had peeled off, the other from the wrist.

A histological study of relevant sections was reported on by Dr. H. Lurie as follows:

A section of the specimens from the kidneys showed a lower nephron nephrosis, of the specimen of skin from the wrist solid hyperkeratosis (Fig. 2). The stratum granulosum was present. The rete Malpighii showed papillary acanthosis. The papillae appeared to be compressed. In the dermis there were numerous sweat glands and a few follicles. The amount of elastic tissue was markedly diminished. Section of the specimen of skin from the neck showed slight hyperkeratosis. The stratum granulosum was increased in thickness and the cells appeared to be keratinized. The rete Malpighii showed acanthosis and dyskeratosis resembling that of a keratoma. In addition there was a small suprabasal cleft. In the dermis there were a few sweat glands and follicles. There was a slight diminution in the amount of elastic tissue.

FIG. 2.—Section of skin from the wrist.

Discussion

This infant is the second case of harlequin foetus seen in this hospital within six months, in itself a remarkable occurrence. The first case has been reported elsewhere (Kessel and Javett, 1955).

The name 'harlequin foetus' is applied to these infants either because of the clown-like appearance of the face with the round O of the mouth or, more probably, because of the deep fissuring of the skin, often with diamond-shaped or triangular plaques of hyperkeratotic epidermis which give the impression of a harlequin's costume. The fissures are found most commonly in areas of movement and are, therefore, found predominantly in the body folds, *i.e.*, the groins, axillae, neck, and over joints. Movement of other parts of the body will cause them to appear in other sites. The hyperkeratosis and inelasticity of the skin cause deformities of the limbs and the infants lie with their arms flexed at the shoulders and elbows and the legs flexed at the hip and knee. The wrists, fingers, ankles and toes may also be held in the flexed position, as, indeed, they

were in our case. The eyelids are everted and a severe degree of ectropion exists. Hair is not present or is very sparse. Hyperkeratotic bands may encircle fingers and toes and impair their blood supply.

The skin may peel leaving a reddish, fairly normal-looking skin underneath, but this layer also hardens and loses its suppleness after a short time, with the eventual reiteration of the original appearance. Our case did not live long enough for the whole cycle to occur, but areas of desquamation did appear with skin underneath which did not appear grossly abnormal. In this respect the harlequin foetus differs from those cases of 'collodion skin' described by Finlay and Bound (1952) and others, in which the desquamation of abnormal skin leaves normal epidermis underneath. The abnormal skin of the harlequin foetus has been compared by various authors to a variety of objects, *viz.*, baked apple or sucking pig, boiled potatoes, the bark of a tree, pieces of parchment, a loosely-built wall, morocco leather, a coat of mail, armadillo or tortoise, elephant skin, rhinoceros skin, crocodile leather or lizard skin (MacLaverty and Kidney, 1952).

The pathological lesion is hyperkeratosis of the epidermis with no, or a grossly deficient, stratum granulosum. The prickle layer is thin. The cutis is normal except for dilated sweat ducts and acini. This is probably due to the fact that the ducts are occluded by hyperkeratosis.

The familial aspect of the disease is apparent in this case as the infant under discussion is not the first in the family suffering from the disease. This has been noted before by Thomson and Wakeley (1921), d'Oelsnitz, Vichier, Chabert and Vigneron (1952) and Sutton and Sutton (1939).

It has been noted at necropsy that the thyroid gland may be rudimentary (Thomson and Wakeley, 1921) and, therefore, treatment with thyroid has been recommended. One feels that this is a somewhat forlorn hope as no treatment appears to be of any avail (Sutton and Sutton, 1939). No connection with congenital syphilis has been noted and in our case the blood Ide test was negative. Treatment, therefore, should be symptomatic, *i.e.*, aimed at amelioration of the skin lesion, prevention of hyperpyrexia and prevention of infection in the deep cracks in the skin. It must be remembered that feeding may be difficult due to the deformity of the mouth.

The prognosis is hopeless as all patients die very young. MacLaverty and Kidney (1952) state that their case and one other in the literature, both of which lived to 6 weeks, are the longest-lived of reported cases.

The cause of death is not generally noted. Lattuada and Parker (1951) state that death is usually due to hyperpyrexia, infection or metabolic disturbance. In view of the necropsy findings in their case and in the case of Kessel and Javett we did blood urea estimations on our patient on the second and the fourth days of life. These estimations disclosed a severe and progressive degree of renal impairment which was borne out by the microscopical findings at necropsy. The cause of the lower nephron nephrosis is difficult to assess. It is possible that there may be tubular damage from hyperpyrexia, although the rectal temperature in our case was never elevated, or that the splinting of the chest by the thick skin may lead to insufficient oxygenation of the blood and kidney damage subsequent to the hypoxia (Kessel and Pepler, 1955).

Summary

A case of harlequin foetus is reported and a brief review of the literature given. It is noted that this case and another reported from this hospital showed lower nephron nephrosis at necropsy.

We would like to thank Dr. K. Mills, Medical Superintendent of the Johannesburg Group of Hospitals, Dr. A. E. Strawbaun, former senior paediatrician to the Transvaal Memorial Hospital for Children, for permission to record this case, Dr. Sher of Johannesburg, for the colour photographs, and Dr. H. Lurie for his histological reports.

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RUPTURE OF THE STOMACH IN THE NEWBORN DUE TO CONGENITAL DEFECTS IN THE GASTRIC MUSCULATURE

BY

P. C. MACGILLIVRAY, A. M. STEWART and A. MACFARLANE

From the Eastern General Hospital, Edinburgh

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Gastric perforation in the newborn is rare. In the infant described here it occurred because there were defects in the wall of the stomach, and the case is reported because of the help it may give in the management and understanding of similar emergencies.

Case Report

A male infant weighing 5 lb. 7 oz. (2·49 kg.) was delivered spontaneously after a normal labour. He was the mother's second child; the pregnancy was uneventful and labour began at term.

At birth the infant was pale and respirations were laboured. A few hours after delivery he vomited about 2 ml. of altered blood and was therefore given 10 mg. of vitamin K intramuscularly. With warmth and the administration of oxygen there was an improvement in his condition, which was maintained the next day though he remained limp and reluctant to feed.

Forty-eight hours after delivery the infant was still not feeding well, and 1 oz. of expressed breast milk was given through an intragastric rubber tube. A similar feed was given three hours later. Following it, he vomited and the abdomen was noted to be a little distended. The vomitus consisted largely of milk, but there were a few streaks of fresh blood in it. Three hours later a further tube feed was given, and shortly after this the baby collapsed. He was pale and the abdomen was grossly distended and tympanitic. The scrotum was large and translucent. With pressure it emptied of gas with a gurgling sound, and filled again when released. Crepitant subcutaneous emphysema was felt in the lower abdominal wall extending from the pubis to the umbilicus, mainly on the left side.

Plain radiographs were taken in the erect and inverted positions (Figs. 1, 2, 3, 4). These showed a gross pneumoperitoneum with gas in the scrotum and in the subcutaneous tissues of the lower abdominal wall. There was some free fluid in the peritoneal cavity and gas was clearly seen in the lower sigmoid colon and rectum.

The clinical and radiological evidence of such a large pneumoperitoneum without an intestinal obstruction suggested a high perforation, probably of the stomach.

At laparotomy (Mr. J. J. Mason Brown) gas under considerable tension escaped and the peritoneal cavity was seen to contain bile-stained fluid with a few flakes of milk. A rupture of the stomach was found which extended over the anterior wall from the greater curvature to the lower oesophagus. The upper half involved all coats of the gastric wall, but in the lower half the mucosa was intact. This rupture was closed with silk sutures without great difficulty, though it was noted that the gastric wall was thin and the sutures were liable to cut out. After the operation the infant's condition was

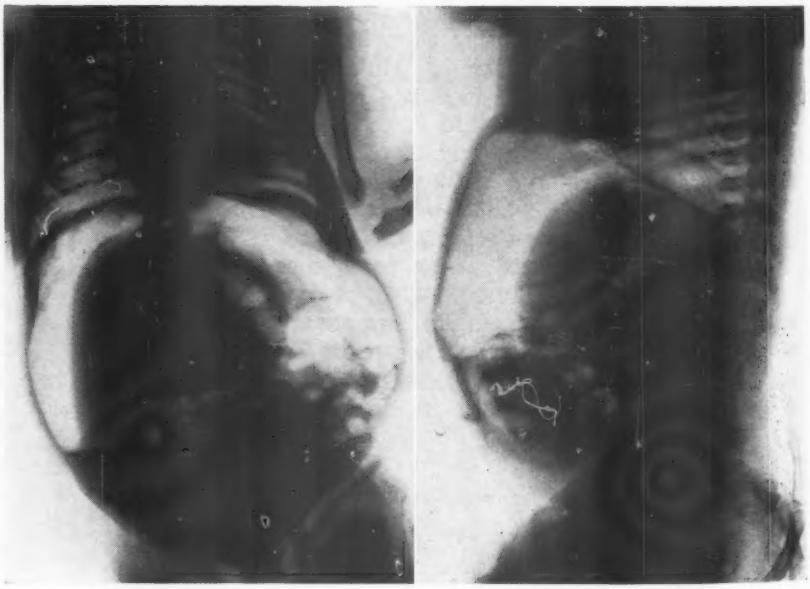

FIG. 1. FIG. 2.

FIGS. 1 and 2.—Radiograph, antero-posterior and lateral, in the erect position, showing gross pneumoperitoneum and intraperitoneal fluid level.

FIG. 3.

FIG. 4.

FIGS. 3 and 4.—Radiograph, antero-posterior and lateral in inverted position, showing gas in the scrotum and in the subcutaneous tissues of the lower abdominal wall.

fairly good, but it rapidly deteriorated, and he died 27 hours later. During the post-operative period no urine was passed despite adequate hydration maintained by intravenous fluids.

NECROPSY. The subcutaneous emphysema was still present in the lower abdominal wall and scrotum. The repair of the rupture in the anterior wall of the stomach was perfectly sound and there was no peritonitis. Histological examination showed that in all parts of the stomach wall the muscle coat was thinner than normal though this was more evident in the body and cardia than in the pyloric antrum. In the body the outer longitudinal coat was extremely thin and in places completely absent. The circular muscle was also considerably thinned, and in several sites there were complete gaps in the circular and longitudinal coats. The stomach wall in such areas was composed only of mucosa, muscularis mucosa and the loose connective tissue of submucosa and subserosa (Fig. 5). At the cardia the oblique fibres were scanty. In the pyloric antrum the circular and longitudinal muscle coats were better developed and thicker than in the body though they were still thinner than normal.

FIG. 5.—Histology of the gastric wall, showing areas of deficient gastric musculature.

The urinary tract had multiple developmental abnormalities (Fig. 6). A congenital bicuspid valve was present in the posterior urethra just distal to the verumontanum. The bladder was considerably hypertrophied but not dilated. The ureters were elongated and tortuous as a result of hypertrophy and dilatation. The ureteric pelves were not dilated. A stricture at the pelvi-ureteric junction on each side was impermeable to the finest probe and would have been thought to be a complete atresia but for the fact that the bladder contained a little urine.

Both kidneys were very small, each measuring 1·5 ×

FIG. 6.—Necropsy specimen of the urinary tract, showing small kidneys, dilated ureters, hypertrophied bladder and urethral valve.

0·8 cm., and several small cysts were present in the cortices. Microscopically both kidneys showed defective development. Glomeruli were fairly numerous and comparatively normal. The secretory tubules were dilated and the collecting tubules were much reduced in number, most of the medulla being occupied by cellular connective tissue. Numerous cysts were present in both cortex and medulla and there were small masses of cartilage in the cortex (Fig. 7).

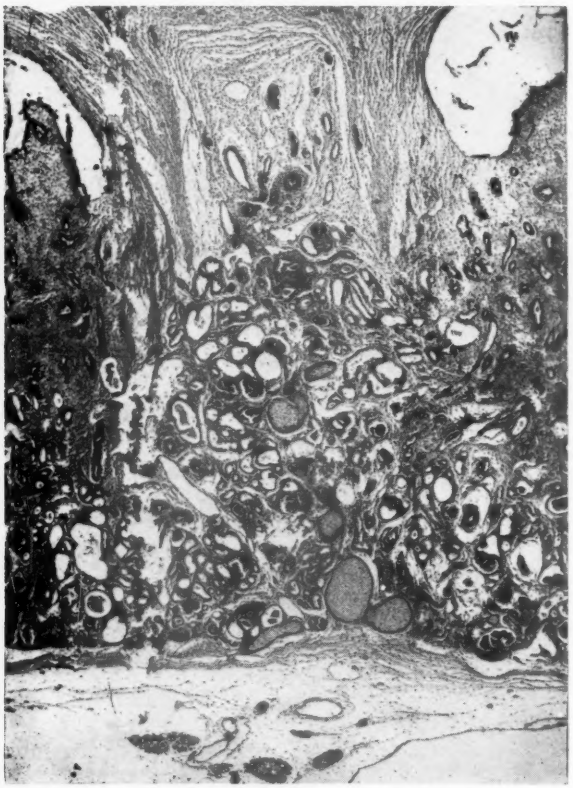

FIG. 7.—Histology of the kidney, showing cysts, dilated tubules and small masses of cartilage.

Discussion

Congenital abnormalities of two systems were present in this infant. Those involving the urinary tract were so severe as to cause death despite successful closure of the ruptured stomach. The facies characteristic of severe renal abnormalities first noted by Potter (1946, 1952a) was not seen in this case, but because of the anuria some gross renal disturbance was suspected.

There appear to be three causes of gastric perforation in the newborn. It may follow acute ulceration, though haematemesis is a more usual complication (Bird, Limper and Mayer, 1941; Guthrie, 1942). It may occur in congenital pyloric or duodenal atresia where there is distension of the stomach (Greene and Gose, 1953). Finally, it may be due to congenital muscle defects in the gastric wall. First described by Herbut (1943). More recently Braunstein (1954) reported five cases and referred to eight others. Since then successful surgical treatment of this type of perforation has been recorded (Northway, DeLano and Claytor, 1954). Morison (1952) considers that careful study of cases of alimentary perforation in this age group has led to more frequent recognition of localized congenital defects in the wall.

Perforation of the normal stomach has followed tube feeding (Potter, 1952b), but it is hard to believe that this could occur when a rubber tube is used with care, though it may happen with one made of polythene. Using a number 6 EG Jacques rubber catheter, stabilized by passing it through a narrow glass tube, we were unable to exert sufficient pressure to tear tissue paper. Nevertheless, rupture may occur when infants with defective gastric musculature are tube-fed, possibly by direct trauma, but more probably by sudden distension, and it seems likely that this happened in our case. Similarly, intragastric oxygen may be dangerous. It would be unreasonable to withhold these valuable procedures because of the remote risk of perforation of an abnormal stomach, but this danger should be remembered.

As there is always gas in the stomach, some usually escapes when gastric or duodenal perforation occurs. Large amounts of gas in the peritoneum will usually indicate a high perforation unless there is also an obstruction, but that this is not invariably so is shown by one of the cases reported by De Vel (1933) when a massive pneumoperitoneum followed rupture of the transverse colon in a newborn infant.

Summary

A case of rupture of the stomach in a newborn infant due to congenital defects in the gastric musculature is described. There were associated anomalies of the renal tract which were gross. The dangers of gastric intubation in such a case are mentioned. Radiological evidence of a massive pneumoperitoneum assisted in making a diagnosis.

We wish to thank Dr. J. O. Forfar and Mr. J. J. Mason Brown for permission to publish this case, and Dr. A. R. Macgregor for her very considerable help.

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FAMILIAL PITRESSIN-RESISTANT DIABETES INSIPIDUS WITH MENTAL DEFECT

BY

B. H. KIRMAN, J. A. BLACK, R. H. WILKINSON and P. R. EVANS

From The Hospital for Sick Children, Great Ormond Street, the Fountain Hospital, Tooting, and Guy's Hospital, London

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Diabetes insipidus resistant to the injection of antidiuretic hormone (pitressin or A.D.H.) is a rare disease which during the past 10 years has been recognized to be different from classical diabetes insipidus. Warkany and Mitchell (1939) reviewed hereditary diabetes insipidus but made no clear distinction between hypothalamo-pituitary and renal cases. Some of the early cases were found to be pitressin-resistant, *e.g.*, those of Bailey and Bremer (1921), but the separate nature of the conditions was not clearly shown until 1945, when Waring, Kajdi and Tappan described

> 'six children with the following features: onset after birth, erratic and unexplained fever, persistent constipation, vomiting in the first three months of life, polydipsia and polyuria not responsive to pitressin, high values for serum sodium and chloride, high skin resistance, rapid dehydration if fluids are restricted or withheld, inability to excrete urine of high specific gravity, familial incidence and occurrence in boys only'.

Their paper admirably summarizes the essential features and avoids confusion with ordinary diabetes insipidus by being entitled 'A Congenital Defect of Water Metabolism'. We report here another family containing children with the same disorder, associated with mental defect.

Family History

The remote family history is scanty, but a maternal great-grandmother of our patients was said to be mentally backward and eventually developed depression and entered a mental hospital. Her husband was said to have suffered from a condition resembling diabetes insipidus and to have died at the age of 40. Of their 13 children, only three survived infancy. One was the grandmother of our patients; her daughter married the father who was healthy and was 22 years older than his wife. He was Rh positive, she was Rh negative, and the second, third and fourth children were Rh positive (Table 1). During the fourth pregnancy her blood was found to contain D antibodies but none of the children had clinical signs of erythroblastosis foetalis, nor did necropsy on the fifth child, who died 24 hours after birth, show evidence of it.

The Children

Case 1. The first child (G.C.) was a boy who died in The Hospital for Sick Children at 18 months. At 6 months he had failed to gain weight and lacked appetite; he weighed only 10 lb. when he died, his maximum weight having been 14 lb. 6 oz. He was admitted on account of malnutrition. He was thin and pale, with prominent costochondral junctions. The specific gravity of his urine was not tested, but the urine was not found to be abnormal by routine tests. He was noticed to 'pass water well'. The blood urea, on a single estimation, was 40 mg. %. He became dehydrated and was given intravenous fluids after which oedema developed. There was no diarrhoea, but his stools were said to be large and fatty with a total fat content of 44% of dried faeces (on a largely milk diet). Finally he developed mastoiditis and died in spite of mastoidectomy. At necropsy, small subarachnoid and subdural haemorrhages were found, but no abnormality of the kidneys was noted, though they were stated to be pale and flabby.

TABLE 1
BLOOD GROUPS OF FAMILY

Father	O		D	
Mother	O	Fy(a−) Jk(a+)	Cde/cde	MSMs, P+, Lu(a−), K−, Le(a−b+)
G.C.	—		—	
E.C.	O	Fy(a−) Jk(a+)	CDe/cde	MNSs, P+, Lu(a−), K−, Le(a−b+)
R.C.	O	Fy(a−) Jk(a−b+)	CDe/cde	MsNs, P+, Lu(a−), K−, Le(a−b+)
D.C.	O	Fy(a−) Jk(a−)	CDe/cde	MsMs, P+, Lu(a−), K−, Le(a−b+)

Case 2. The second child (E.C.), another boy, also suffered from a wasting disease, and was eventually found to be a case of pitressin-resistant diabetes insipidus.

Pregnancy, birth and the neonatal period were normal. He weighed 8 lb. 14 oz. at birth and was breast fed until he was 4 months old, when he weighed 12 lb. Then he was bottle fed and failed to gain weight; at 6 months he was admitted to The Hospital for Sick Children on account of failure to thrive, constipation and refusal of feeds. He was small, thin and dehydrated; in his case too the costochondral junctions were enlarged. The cerebrospinal fluid was normal apart from a chloride content of 850 mg. % (as NaCl).

He weighed 13 lb. at 9 months and 18 lb. at 16 months. At 21 months he still had cough, vomiting, anorexia, constipation and lethargy. A barium swallow, urine examination and blood count were all normal. Three months later he had a severe upper respiratory infection with a normal blood count and chest radiograph, and a negative tuberculin test (Mantoux 1/1,000). His duodenal juice contained a normal amount of trypsin. The blood sedimentation rate was 52 mm. in one hour (normal, up to 10), and there was a trace of albumin in the urine. After treatment he weighed 18 lb. There was another respiratory infection at 2½ years, when he weighed 19 lb. When nearly 3 years old he broke his left tibia, and at 4 years was admitted to Guy's Hospital with a fractured femur. Between the ages of 3 and 4 years he had some attacks which were thought to be faints. This was his fifth hospital admission, and only then was polydipsia noticed; polyuria was still not obvious as he was incontinent. Attempts to restrain him in order to collect a specimen of urine caused fever, presumably because he stopped drinking, but this was not understood at the time. Blood examination showed a hyperelectrolytaemia. He was obviously mentally defective; he could not talk or feed himself and had not walked without support.

He was in much the same state when re-admitted to The Hospital for Sick Children for investigation at 4 years and 5 months. This admission was prompted by the findings of hyperelectrolytaemia and resistance to pitressin in his younger brother (D.C.). He was transferred to the Fountain Hospital after investigation and confirmation of the diagnosis.

He was an imbecile. He stood with difficulty, holding on for support. He could not feed himself with a spoon or bread and butter, but would hold a cup. He did not talk or dress himself. He saw and heard. He was doubly incontinent. He obeyed simple instructions. On the Vineland Social Maturity Scale his developmental quotient was 31. On the Merrill Palmer Scale his intelligence quotient was 37. He was obviously craving for fluid and cried until this want was supplied, avidly seizing a glass and draining it. On one occasion he drank four glasses full of water in rapid succession—approximately a litre. No epileptic attacks occurred whilst in hospital.

Physically he was in poor general health with a striking generalized pallor, thin, listless, with marked infantilism and hypotonia but no specific neurological abnormalities. He had purulent rhinorrhoea and intermittent low pyrexia. He had several attacks of pneumonia, otitis media and enteritis. He rarely remained well for more than a few weeks. The skull circumference was 18½ in. The ocular fundi appeared normal. The blood Wassermann reaction, Kahn and Meinicke tests were negative.

Two years later the intelligence quotient (Merrill Palmer) was unchanged; he could walk and run and could form short sentences. The electroencephalogram was within normal limits.

The following investigations were carried out on E.C.

RADIOGRAPHS. When aged 4 years the long bones were slender, the femora and tibiae were slightly bent, as in fragilitas ossium, but rickets was not present. The rib ends were expanded a little but not abnormally. There was a fracture of the femur. The skull was normal and the pituitary fossa was well formed. Bone age and ascending pyelography were normal.

BLOOD CHEMISTRY. When the child was aged 4 years 5 months the blood chemistry was: blood urea 52 mg. per 100 ml., serum sodium 150 m.Eq./l., serum potassium 5·0 m.Eq./l., plasma chlorides 109 m.Eq./l., plasma bicarbonate 27·9 m.Eq./l.

URINE. Urine examination showed no abnormality except for a trace of protein, and a specific gravity of 1,004 after 12 hours' fluid restriction. The amino-acid excretion was normal and no phenyl pyruvic acid was found.

PITRESSIN TESTS. Two tests were carried out, the first with a dose = 0·25 units at 4 p.m. when the blood urea level was 31 mg. %, the second after a dose = 2·5 units at 12 noon.

First pitressin test

Time	S.G.	Volume (ml.)	Urea Clearance (% average normal)	Chloride Concentration (m.Eq./l.)	Chlorides/Hour (m.Eq.)
3–4 p.m.	1,004	89	76	15·6	1·39
4–5 p.m.	1,003	116	65·5	14·5	1·73
5–6 p.m.	1,003	106	68·5	14·5	1·58
6–7 p.m.	1,005	81	71·7	15·6	1·26

Second pitressin test

Time	S.G.	Volume (ml.)	Chloride Concentration (m.Eq./l.)	Chlorides/Hour (m.Eq.)
11–12 noon	1,006	118	21·9	2·58
12– 1 p.m.	1,006	129	18·8	2·43
1– 2 p.m.	1,006	162	19·8	3·21
2– 3 p.m.	1,006	146	15·6	2·27

Case 3. The third child, also a boy, did not suffer from diabetes insipidus or mental defect. When seen at 4 years of age he was in good health, except for slight talipes equino-varus.

Case 4. The fourth child (D.C.), again a boy, was born after surgical induction and weighed 8 lb. 8 oz. His mother had Rh antibodies up to 1/16, but the baby had what appeared to be physiological jaundice, with normal serological tests, haemoglobin and serum bilirubin. Nevertheless he became anaemic and was given a blood transfusion at 3 months. At 4 months his haemoglobin level was 10·5 g. %. He was early noted to be retarded. At 8 months he was admitted to Guy's Hospital. At the time he could not sit up. He was thought to have rickets but the biochemical and radiological findings did not support this. His urine was constantly of low specific gravity but was otherwise normal. His blood chemistry showed a raised urea with a high serum sodium content. On one occasion the blood phosphorus level was raised (10·4 mg. %), but later it was found to be normal. While in hospital he was given 35-45 oz. of fluid daily. At 14 months he was admitted to The Hospital for Sick Children for further investigation. On admission he was a pale, apathetic, dehydrated and wasted child who took little interest in his surroundings. He was unable to sit and muscle tone was poor. His weight was 13½ lb. and height 26½ in. While in hospital he had breath-holding attacks. He took fluids eagerly but was liable to vomit if given too much fluid at one time. At first he had a fever of 99° to 100°, but when his fluid intake was adequate the temperature settled. During the seven weeks after his admission to hospital he gained 5½ lb., of which 2 lb. were in the first two weeks. His intake at this time was about 130 oz. daily and on occasions he took as much as 185 oz. in one day. While taking this large amount (he had not been having a very large intake at home) his condition began to improve. Slowly, he appeared brighter and began to look like a normal child. At 19 months he was tested and found to have a level of development of 9 to 10 months. His motor power improved also, and he was soon able to sit up, and later began to walk round his cot. A low-salt diet was tried for a short time in an effort to find some method of reducing his water requirement. However, he did not appear so well on this régime. When finally discharged at the age of 22 months he weighed 22 lb. He was followed up in the Out-patient Department and continued to gain weight. At the age of 26 months, he was tested again in the Department of Psychological Medicine. He had made definite progress but was still retarded. He was able to walk and could say a few single words. A year later he was re-tested and had made further progress, but was still not of normal intelligence. A fourth test was performed at the age of 4 years 3 months. On this occasion a formal assessment of his intelligence was attempted, and he was considered to have an I.Q. between 63 and 68.

INVESTIGATIONS. These were the following:

At the age of 8 months an intravenous pyelogram showed poor concentration of dye.

Blood Chemistry. The following results were obtained:

Age	Blood Urea (mg. %)	Serum Sodium (m.Eq./l.)	Serum Chlorides (m.Eq./l.)	Plasma Bicarbonate (m.Eq./l.)	Serum Potassium (m.Eq./l.)	Blood Phosphorus (mg. %)
8/12	64	—	—	—	—	10·4
	80	—	—	—	—	4·4
		172	114			
	75	168	120	29		
9/12	51	—	124	35	—	—
14/12	76	175	115	31	5·1	
	53		109	26	4·2	

Urine. The specific gravity was never above 1,012, but otherwise the urine was normal, as was also the amino-acid pattern.

Renal Function Tests. At 9 months the urea clearance was as follows:

Time	Urine (vol. ml.)	Urine ml./min.	Blood Urea	Urine Urea (mg. %)	Urea Clearance
1 hr.	22	0·37	59	705	28% of average normal (standard)
1 hr.	22	0·37	59	580	22% of average normal (standard)

Pitressin tests were performed three times.

(1) At 9 months, when the dose was 2 units at 11.30 a.m.

(2) At 15-18 months when the dose was 0·165 units at 3.45 p.m.

(3) The third test was done after a dose of 1·65 units at 12 noon, when the blood urea was 76 mg. %.

(4) The dose was 0·08 units at 11.30 a.m.

(5) A fifth test was done using a control period after the injection of 1 ml. normal saline at 3.15 p.m., when blood urea was 46 mg. %.

The fifth child was born after labour had been induced early because of the mother's antibodies, and died on the second day. At necropsy death was attributed to atelectasis.

First pitressin test

Time	S.G.	Volume (ml.)	Urea Concentration (mg. %)
10 –11.30	1,012	54	890
11.50–12.45	—	12	830
12.45– 3.5	1,012	19	1,030
3.10– 4.25	1,004	18	890

Second pitressin test

Time	S.G.	Volume (ml.)	Chloride Concentration (m.Eq./l.)	Chloride Excretion/Hour (m.Eq.)
2.45–3.45 p.m.	1,004	22	20·8	0·46
3.45–4.45 p.m.	1,002	17	14·5	0·25
4.45–5.45 p.m.	1,004	32	17·6	0·56
5.45–6.45 p.m.	1,006	137	19·8	2·71

Third pitressin test

Time	S.G.	Volume (ml.)	Urea Clearance of Average Normal	Chloride Concentration (m.Eq./l.)	Chloride Excretion/Hour (m.Eq.)
11–12 M.D.	1,009	23	55 (standard)	19·1	0·44
12– 1 p.m.	1,009	34	65 (maximum)	17·1	0·58
1– 2 p.m.	1,007	65	65 (maximum)	48·9	3·18
2– 3 p.m.	1,003	19	40 (standard)	24·4	0·46

Fourth pitressin test

Time	S.G.	Volume (ml.)	Chloride Concentration (m.Eq./l.)	Chloride Excretion/Hour (m.Eq.)
10.30–11.30	1,003	115	5·1	0·59
11.30–12.30	1,001	179	9·2	1·65
12.30– 1.30	1,001	80	12·3	0·98
1.30– 2.30	1,000	225	24·6	5·55
2.30– 3.30	1,001	125	15·4	1·92
3·30– 7.30	1,000	253	23·8	6·02

Fifth pitressin test

Time	S.G.	Volume (ml.)	Urea Clearance (% of normal)	Chloride Concentration (m.Eq./l.)	Chloride Excretion/Hour (m.Eq.)
2.15–3.15 p.m.	1,002	110	70 (maximum)	10·2	1·12
3.15–4.15 p.m.	1,002	160	88 (,,)	11·3	1·81
4.15–5.15 p.m.	1,002	118	60 (,,)	14·3	1·69
5.15–6.15 p.m.	1,002	170	90 (,,)	11·3	1·92

Discussion

Interpretation of Renal Function Tests. Unfortunately no renal function tests were done on the first child (G.C.) and we know only that his blood urea was 40 mg. % on one occasion. In the two other children (E.C. and D.C.) described in this paper, a number of tests of renal function were performed.

In D.C. it was shown that the urine specific gravity rose only to 1,004 after 12 hours' fluid restriction, showing a serious defect in concentrating power. Since it was suspected that he had normal glomeruli, with a renal tubular defect for water reabsorption, it was decided to carry out a combined pitressin test and urea clearance. We considered that the slightly raised levels of blood urea obtained during the early investigation were a reflection of a reduced glomerular filtration rate secondary to dehydration. We therefore took care to supply abundant water during the tests. The injection of pitressin is purely a test of the ability of the renal tubule to react to circulating pitressin (A.D.H.) by a reduction in volume of urine, with a rise in specific gravity and a corresponding rise in the concentration of solutes, of which urea and chloride (as sodium chloride) are most conveniently measured. In general the results obtained with the pitressin test run more or less parallel to those obtained by the fluid restriction test, but the highest specific gravity obtained after the injection of pitressin is usually 1,015-1,020 and is always less than the maximum specific gravity after 12-hour fluid restriction. The reason for this difference between the results of the two tests is not known. As the kidney is extremely sensitive to pitressin a maximal response is obtained with very small doses. We have used water-soluble pitressin (Parke-Davis), which is almost free from

the oxytocic factor, and which we found active in normal children in a dosage of 0·5 units per square metre of body surface area. This is much less than that recommended by Behrendt (1949) on the basis of the work of Sodeman and Engelhardt (1942) and Schneeberg, Likoff and Rubin (1943), but is twice the largest dose used by Heller (1944). Large doses may, in fact, give misleading results by interfering with glomerular filtration, and undesirable side-effects such as pallor and slight hypertension may occur.

In doing this series of investigations we first used a dose calculated as described above and later used larger doses in order to eliminate the possibility of partial insensitivity. In conditions such as true diabetes insipidus and in the pitressin-resistant type, the urine passed during the control period (before the injection of pitressin) is bound to be low in specific gravity, and an unvarying flow can be obtained only by keeping the water load constant during the test. This was done by dividing the daily intake by 12 and giving this amount hourly. In the normal controls it is, of course, necessary to inhibit the production of endogenous pitressin (A.D.H.) by maintaining a similar water load throughout the test in order to demonstrate the effect of the injected pitressin.

Results

E.C. The first test with 0·25 units of pitressin, *i.e.*, 0·5 units per sq. m. surface area, has been compared to a similar test using the same scale of dosage on a child of the same age with normal kidneys. The difference between the two is very striking. Urea clearances were calculated from the data obtained during the first pitressin test and showed low normal figures. (The clearances are first calculated in absolute figures, then recalculated for a surface area of 1·73 sq. m. and the figure obtained is then expressed as a percentage of a normal adult figure.) A second test with 10 times the original dose gave similar results. We considered that these results demonstrated that glomerular filtration was normal, but that the tubular response to pitressin was lacking.

D.C. His first urea clearance tests, done when he was 9 months old, gave the very low values which might be expected if he were slightly dehydrated; in support of this is the fact that his blood urea varied at this time between 59 mg. % and 80 mg. %. Also the diagnosis had not been substantiated and he was being given inadequate amounts of water to drink. Similar difficulties arose in the interpretation of the first pitressin test, which was done during the same admission. The later pitressin tests, with smaller doses, were a little more satisfactory, but owing to inconstant water loads during the test the flow of urine obtained was very variable. Nevertheless, it was possible to demonstrate a failure of response to pitressin in three different doses. The most satisfactory of the tests, from the point of view of urine flow, was that performed with 1 ml. of normal saline to see whether the actual prick of the injection had any influence on the flow. We did this control test because it has been found that discomfort, such as is produced by catheterization, particularly in boys, causes a considerable reduction in urine flow for about one to two hours. However, the urine flow obtained during this last test was even, and the urea clearance was shown to be unequivocally normal. The pitressin test done on a standard dosage scale (dose: 0·165 units) has been compared (see graph) with a similar test performed in a child of the same age, with normal kidneys.

Both patients showed pyrexia when dehydrated, which has been commented upon previously (Waring *et al.*, 1945; Luder and Burnett, 1954). Presumably this fever is analogous in some way to dehydration fever in infants, but the mechanism is not understood. The younger child (D.C.) also showed an undue liability, when compared with controls, to become pale even after small doses of pitressin. Such a sensitivity to the side-effects of pitressin was noted by Williams and Henry (1947) who thought that the kidney might not be destroying or fixing the pitressin as rapidly as usual.

The precise cause of the condition has not been fully worked out. The most likely alternatives are an anatomical defect in the region of the tubule responsible for water reabsorption, or an 'end-organ insensitivity'.

Anatomical Defect

Macdonald (1955) reported that micro-dissection of the kidneys of a 4½-month-old infant with this condition showed some diminution in the proximal tubular convolutions. The distal tubules and loops of Henle were normal in appearance and length. Darmady and Stranack (1954) dissected the tubules of one of another series of cases studied at Great Ormond Street. He reported no evidence of atrophy of the collecting or distal tubules. The proximal convoluted tubule seemed shorter than normal, but there appeared to be no abnormality of structure.

Although no abnormality has been detected in the structure of the tubule it is possible that the relation of the loops of Henle and the collecting tubules and their adjacent blood vessels in the renal medulla may be unusual as a congenital defect.

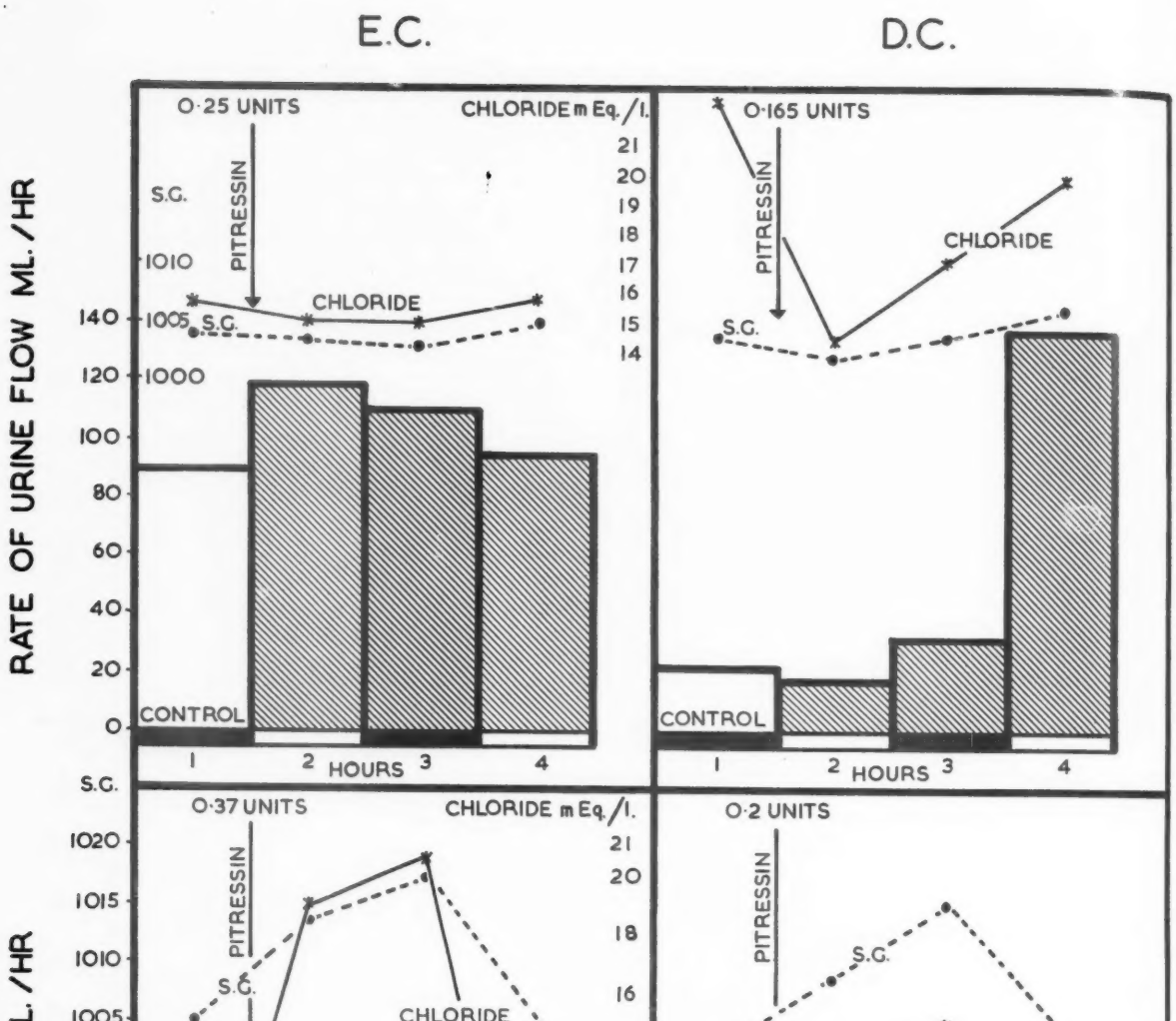

FIG. 1.—The effect of the standard dose of pitressin on the urine volume and concentration of patients E.C. and D.C. compared with normal controls.

The importance of these relations is stressed by the work of Wirz, Hargitay and Kuhn (1951). They showed that in the golden hamster papillary blood vessels adjacent to the long loops of Henle contained hypertonic blood when the kidney was producing hypertonic urine. They suggested that the loop of Henle acts as an active hairpin counter current system, causing an increased concentration of solutes in the tip of the loop. These hypertonic media, which are some distance away from the convoluted tubules situated in the cortex, could cause passive transport of water from the urine in the collecting ducts which they adjoin and effect the final concentration of the urine. Thus, in the normal hamster, high osmotic pressures in the final urine can be achieved without the occurrence of high osmotic gradients, whereas in the patient with renal diabetes insipidus an anatomical abnormality might make concentration impossible. The relation of this mechanism to the action of A.D.H. is unknown.

'End-organ insensitivity' could be the explanation of the lack of action of A.D.H. if no anatomical defects were present and the hormone were present in adequate amounts in the blood stream.

At present it is not possible to decide which of these possibilities is the explanation of this disease.

Treatment

The treatment of these cases raises several interesting points. The consumption of large quantities of water during infancy, when the child is unable to regulate his own intake, makes the detailed instruction of the mother very important. Also the very large volumes of fluid required are liable to distend the stomach and impair the appetite for solids. It is necessary therefore to spread the fluid intake as evenly as possible during the day and if necessary during the night. The best guide to adequate hydration is the appearance of the child and his look of comfort or discomfort. Daily weighing is not very helpful as the weight is liable to violent fluctuations from day to day, but it is certain that more fluid is required if there is a persistent loss of weight. The rate at which rehydration of a new case should be attempted seems to depend upon each individual. Some observations (Wallace, 1953) have been made in cases similar to those demonstrated here which seem to show that it is better to proceed gradually with rehydration and not to attempt to bring the blood chemistry back to normal too rapidly. A too rapid rehydration may bring on symptoms akin to water-intoxication. This has been supposed to be due to a rapid change in the intracellular osmotic pressure, as the cells seem to take time to adapt to a new level of osmolarity.

Family and Sex Incidence

The familial incidence of pitressin-resistant diabetes insipidus is remarkable. In this family there was one healthy child, while two had the condition, another had an unidentified wasting disease, and the last died too young to show diabetes insipidus. Unfortunately, we do not know whether the great grandfather also had it.

Both the affected children were males and similar cases which have been previously reported have been male. Where members of more than one generation were affected (Williams and Henry, 1947; Forssman, 1945; Flax and Gersh, 1955) transmission was through the female as a dominant sex-linked characteristic. The condition is not necessarily fatal, some of the patients having reached adult life (Williams and Henry, 1947; Cates and Garrod, 1951), but no case of father-to-son transmission has yet been recorded. Although there is no proof, it is tempting to suppose that in our family the great-grandfather did, in fact, have pitressin-resistant diabetes insipidus, and that some of his sons, all of whom died in infancy, also had it, while a surviving daughter passed it on to our patients.

Mental Defect

Our two patients were mentally defective, as was that described by Luder and Burnett (1954), while one member of the family described by Williams and Henry (1947) was retarded (he did not sit up until he was 1 year old) and had the disease. From records of other cases, it is clear that mental defect is not an essential accompaniment, but it is interesting to speculate whether in severe cases prolonged dehydration can produce it. In our cases we noted a close correlation between the mental state and the adequacy of the fluid supply. In Case 2 the experience of seeing this child alter when he was hydrated was inspiring, for it looked as though a baby who was almost an ament was being endowed with a mind, simply by being given a great deal of water. This improvement in the mental state is presumably largely due to the general increase in physical well-being which results in these patients when they are given adequate amounts to drink. Also when their thirst is unsatisfied their whole consciousness is preoccupied by a desire for fluids. This dehydrated state is further complicated by fever and infections to which they then seem peculiarly liable and which further reduce the energy available for mental activity.

Earlier optimism was somewhat modified by the lack of striking further mental development in these patients when fully hydrated. Case 1 has not developed more rapidly than the average imbecile of

similar grade. From having a developmental quotient assessed at 31 on the Vineland scale and an I.Q. of 37 on the Merrill Palmer he scored some two and a half years later a D.Q. of 29 and an I.Q. of 31 on the Stanford Binet scale. Thus it would appear that in his case there is irreversible damage to the brain such as to give him the expectation of mental development of the unspecified imbecile.

Summary

Two brothers suffered from pitressin-resistant diabetes insipidus. Hydration improved them mentally and physically but did not make them normal. Investigation suggested that glomerular function was normal but that tubular response to pitressin was lacking. Difficulties in understanding, investigating and treating the condition are discussed.

We would like to thank many people for help in these cases over several years, particularly Dr. W. W. Payne for advice on chemical investigation, Dr. C. A. Holman and Dr. R. R. Race for blood grouping, Dr. D. A. Pond for electro-encephalography, Mrs. M. Marrs and Miss M. B. S. Durward for psychological reports, and the Department of Medical Illustration, The Hospital for Sick Children, Great Ormond Street, for the figure.

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BOOK REVIEWS

The Lung. Clinical Physiology and Pulmonary Function Tests. By J. H. COMROE, R. E. FORSTER, A. B. DUBOIS, W. A. BRISCOE and E. CARLSEN. (Pp. viii + 219; 57 figures. 40s.; $5.50.) Chicago: The Year Book Publishers. (Distributed in United Kingdom by Interscience Publishers, Ltd.) 1955.

Up to quite recent times the physiology of the lungs was rarely considered in relation to pulmonary disease, but in the last 10 years there has been a greater interest in clinical pulmonary physiology and the application of lung function tests in the field of thoracic surgery. Unfortunately most treatises on pulmonary physiology are written for physiologists and are too complex for the ordinary doctor or medical student. In this monograph the authors explain the basic facts of pulmonary physiology in a way that the clinician can understand. The mode of presentation is designed for easy reading and there are many illustrations, most of which are schematic and self-explanatory. By confining all the mathematical figures and equations to the end, the reader is able to grasp the meaning without having to absorb the proof, unless he so desires.

The book is divided into three sections. The first describes pure physiology and the theories of various tests of pulmonary function. The authors stress the importance of ventilation, especially alveolar, as opposed to respiration, devoting 37 pages to this important aspect and point out that uneven ventilation of the lung can lead to pulmonary insufficiency even though the total air movement seems adequate. In the second section the application of various pulmonary function tests is discussed and a series of case histories are presented, showing how these tests are of value. The third section has a valuable glossary of physiological terms and definitions and contains all the data and equations regarding the theoretical considerations of ventilation and blood flow, as well as much of the simple physics of gases and liquids.

Although only 219 pages, this book contains all the facts that the average specialist in the thoracic field needs to know about pulmonary physiology. It is not merely a book to have on the shelf, but should be in the pocket.

Pädiatrischer Röntgenatlas. By M. A. LASSRICH, R. PRÉVÔT and K. H. SCHÄFER. Edited by K. H. Schäfer. (Pp. xii + 333; 700 figures. DM. 115.–) Stuttgart: Georg Thieme Verlag. 1955.

This volume of diagnostic paediatric *x*-ray pictures comes more than 20 years after the last German textbook of radiology. During this time, not only has our knowledge increased, but the ability both to take and to reproduce radiographs of the body in health and disease has increased greatly.

The authors of this *Pädiatrischer Röntgenatlas*, which comes from Hamburg and honours the 70th birthday of Professor Hans Kleinschmidt, have the inestimable advantage that the highest class paper has been used for the reproduction of their magnificent collection. The result is a beautiful book, divided into three sections dealing with the thorax, the abdomen and the skeleton respectively. The special techniques used to demonstrate various lesions are not neglected, and the individual pictures are accompanied by clinical and radiological thumbnail sketches which are models of conciseness and brevity. The publishers are as much to be congratulated as the authors on their presentation of this material.

The volume makes no attempt to be a textbook, but amply fulfils its declared intention of being an atlas. While probably its greatest usefulness will be to those principally concerned with paediatric radiology it will make an immediate appeal to paediatricians in general. For the wealth of material included, the book has been kept to a reasonable size, and for the price of 115 German marks it is very good value for the money. As it has been kept so pictorial, no great familiarity with the German language will be necessary for the English reader.

The Pediatric Years. By LOUIS SPEKTER. (Pp. xxv + 734; 21 figures. 90s.) Oxford: Blackwell Scientific Publications.

This book, by the director of the Bureau of Maternal and Child Hygiene of the Connecticut State Department of Health, is intended for professional workers 'in the fields associated with pediatric medicine'. The preface gives a list of 30 examples, including chiropodists, camp directors and sanitary engineers. For such a varied public, it is surely an impossible task to present technicalities at length in non-technical language equally understandable by all, and some sort of 'dictionary' would probably serve the purpose better. However, the author, expressing his indebtedness to a very long list of people, has composed a massive volume in six main sections. The first deals with maternal care and the next with normal growth and development in childhood. Next comes the longest part of the book which is virtually a textbook on diseases of children. Services available (in the U.S.A.) and standards are divided between two shorter sections and a final part describes 'pediatric procedures' and gives a glossary. As a work of reference to be used by non-medical workers the book is not without its dangers, although it has, of course, some value as a source of information of great variety between two covers and therefore easily obtained. Paediatrics in its widest sense has, however, grown too large to be contained adequately in this way.

Obese Children. By FLEMMING QUAADE. (Pp. 302. No price given.) Printed by Danish Science Press Ltd., Copenhagen. 1955.

This book is the expansion of a prize essay on the subject of obesity in childhood, with special reference to Hilde Bruch's theory on the causation of this condition.

Bruch supposed that an ambivalance exists in the attitudes of mothers to their obese children; that they have fundamentally hostile feelings compensated for by more obvious, but more superficial, over-protection and demonstrations of love, manifested by gifts of food.

The book make a careful study of 185 obese children, analysing a variety of data and comparing them with similar data from over 1,000 non-obese children. Dr. Quaade eventually comes to two principal conclusions. First, that almost nothing distinguishes obese children from their slimmer friends other than their fatness, together with a characteristic emotional outlook which is not causative but a result of the impact their obesity makes upon their school friends. He concludes that there is little support of Dr. Bruch's thesis regarding the relationship of parents to their obese children. Secondly, he concludes that the main reason why children become fat is because of their excessive appetites, though he bases his opinions on impressions only.

Dr. Quaade has nothing to offer regarding why some children's appetites lead them to eat more food and lay down more fat than others, and this surely is the crux of the problem which Dr. Bruch made an attempt to solve.

The book is well printed, and though paper backed, is adequately bound. It abounds in tables and charts, and is a useful summary, without making additions to our knowledge, of the statistical facts regarding obesity.

Growth at Adolescence. By J. M. TANNER. (Pp. xii + 212; 57 figures, 10 plates. 32s. 6d.) Oxford: Blackwell Scientific Publications. 1955.

How far is adolescence the concern of the paediatrician? Designers of the earlier children's hospitals evidently considered that childhood ended when puberty began, and planned their wards and ages of admission to keep the pubescent child at bay. Nowadays many children's out-patient departments cooperate with the school medical service in seeing school pupils up to the age of compulsory school attendance, whilst there is strong evidence that each stage of development (including puberty) is being reached earlier than it was 50 or even 20 years ago. The trend has been for paediatricians to take an increasing interest not only in the behaviour problems of early puberty and the aberrations of certain diseases such as tuberculosis and diabetes which are characteristic of this phase of development, but also in the physiology of puberty itself. Dr. Tanner's monograph therefore comes at an opportune time. The author gathers together an immense amount of information from the widely-scattered literature, handles it critically, and presents it in a manner which is generally comprehensible to a reader without expert statistical knowledge. The text is well illustrated by line drawings prepared by Mr. R. H. Whitehouse, and by a number of half-tone plates.

Writing as a human biologist, Dr. Tanner has deliberately excluded from detailed consideration the aspects of adolescent behaviour which he regards as purely culture induced. He adopts Kuhlen's view that adolescence is not to be thought of as an unduly stressful period, but rather as one during which various adjustment problems have to be faced, which produce anxiety and stress. It may well seem to the less casuistic reader that this amounts to the same thing as regarding adolescence as an 'unduly stressful period', and that, since adolescence has inevitably to be experienced in a culture which demands a greater or less degree of control of adolescent drives, it is somewhat artificial in dealing with human material to distinguish between biological and culture-induced behaviour. Minor matters of opinion apart, however, there is no doubt that the author has admirably fulfilled his purpose, and provided a clearly-written and authoritative description of growth during adolescence, which is likely to become a standard text. It is addressed to medical students and their pre-clinical and clinical teachers (amongst others), and will be particularly valuable to those wishing to bridge the gap which commonly exists in the medical curriculum between embryology and the anatomy and physiology of the adult.

Les Explorations Biologiques en Pédiatrie. By C. POLONOVSKI and J. COLIN. (Pp. 500. Fr. fr. 3,900.–.) Paris: Expansion Scientifique Francais. 1955.

In contrast to the all-embracing character of Brock's work, reviewed above, this French work has a more modest range of activity yet contrives to deal with many unexpected aspects of paediatric physiology and biochemistry. Modes of investigation of prominent biochemical disorders are discussed and many technical methods are described in detail.

The authors have divided their book into two major parts. The first is concerned with chemical methods and their results, while the second considers such subjects as acid-base equilibrium, calcium/phosphorus metabolism, kidney and liver function and the endocrine glands, and there is a considerable section on blood coagulation and haemolysis. There is much to be commended in the authors' presentation, their clear descriptions and precise deductions. There are, however, many signs of hasty proof reading, *e.g.*, goagulation for coagulation on p. 7, Chigago for Chicago on p. 55, and spseudo for pseudo on p. 195, mistakes which readily strike the insular English eye, and in any further edition of a book which might well find itself a permanent place in the French literature no doubt these more obvious errors will be corrected.

Incidentally, the cover of the book states that the authors are Colin and Folonovski, while the title page and publishers' note say that the authors are Polonovski and Colin; possibly in this manner honour is satisfied, but not in a way which will commend itself to the constructors of alphabetical indexes.